Journal of Regenerative Biology and Medicine
An Open Access Journal
ISSN: 2582-385X

Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy

Konghua Lin*
Olympus Corporation, Daiwa Sasazuka Tower, 1-50-1 Sasazuka, Shibuya-ku, Tokyo 151-0073, Japan

***Corresponding Author:** Konghua Lin, OlympusCorporation, Daiwa Sasazuka Tower, 1-50-1 Sasazuka, Shibuya-ku, Tokyo 151-0073, Japan, Tel: 03-5738-3959, Fax: 03-5738-3966

Received Date: 12-16-2019; **Accepted Date:** 1-14-2020; **Published Date:**01-20-2020

Abstract

Osteoarthritis has huge impact on medical care system and finance as its large patient populations and its increasing contribution to the chronic disability in age population. Increasing effort to develop new treatment of osteoarthritis with cell therapy is being made. In this paper, we review cell sources, inclusion criteria and delivery method of cell therapy for osteoarthritis in the current clinical studies, and discuss the possibility to improve the clinical outcome.

Keywords

Cell therapy; Osteoarthritis; Regenerative rehabilitation; Cell sources; Inclusion criteria; Delivery methods

Abbreviations

OA: Osteoarthritis; ADSCs: Adipose tissue-derived mesenchymal stem cells; SVF: Adipose-derived stromal vascular fraction; BMAC: Bone marrow aspirate concentrate; ACI: Autologous chondrocytes implantation; PRP: Platelet-rich plasma

Introduction

More and more attention is being paid on osteoarthritis because its large patient populations and huge burden on health care society and finance. Osteoarthritis (OA) is already one of the ten most disabling diseases in developed countries [1]. It is estimated that at least 27 million people across the United States of America are affected by arthritis, with an estimated total annual cost to the US economy of $89.1 billion US dollars [2], and the globalage-standardized prevalence of knee OA was 3.8% in 2010 [1]. This number is much higher in

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

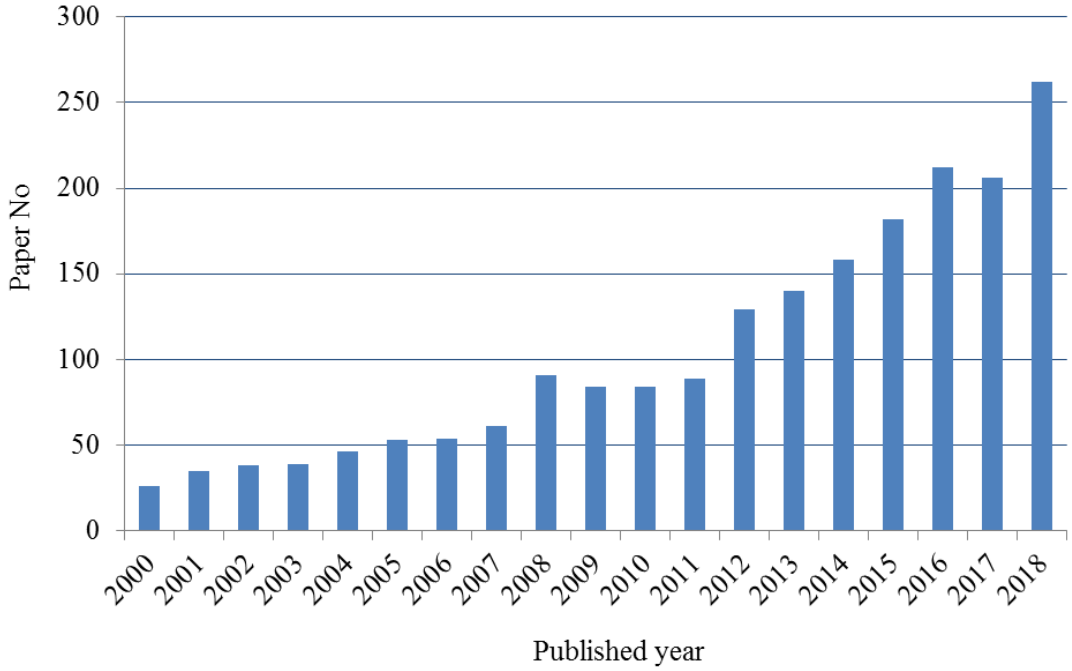
some developing country, such as China. The prevalence of knee OA was reported to be 8.8% (men: 6.3%, women: 11.0%) in China [3]. With the increase of population age, the prevalence is likely to further increase. Worldwide estimates that 9.6% of men and 18.0% of women aged over 60 years have symptomatic osteoarthritis.80% of those with osteoarthritis will have limitations in movement, and 25% cannot perform their major daily activities of life [1]. Based on the Lay version of the OARSI definition of osteoarthritis, "Osteoarthritis is a disorder that can affect any moveable joint of the body, for example knees, hips, and hands. It can show itself as a breakdown of tissues and abnormal changes to cell structures of joints, which can be initiated by injury [4]. Currently, diagnosis of OA is based on plain radiography, which was described by Kellgren and Lawrence (KL) in 1957 [5]. Each radiograph was assigned a grade from 0 to 4, which correlated to increasing severity of OA, with Grade 0 signifying no presence of OA and Grade 4 signifying severe OA [5].

There are several methods available to treat OA based on the degree of the disease, including conservative treatments such as pharmacologic management [6], surgical interventions such as high tibial osteotomy (HTO) [7] and total knee arthroplasty (TKA) [8]. With the development of regenerative medicine, a less invasive procedure cell therapy is being developed.

PubMed advanced search function (https://www.ncbi.nlm.nih.gov/pubmed/advanced) was used to find the papers regarding cell therapy for OA (Key words: cell therapy; osteoarthritis) from 2000 to 2018, and results are showed in (Figure 1).The papers published yearly are increased from 26 in 2000 to 262 in 2018, indicating increasing effort is being made to develop new treatment to fight OA. Regarding to cell therapy for osteoarthritis, several excellent reviews were recently published [9-11]. Freitag J et al. summarized current available regenerative techniques, including autologous chondrocyte implantation (ACI), mosaicplasty, micro fracture, MSCs [10]. Jevotovsky D.S. et al reviewed treated 2,390 patients with MSCs and concluded that while studies support the notion that MSC therapy has a positive effect on OA patients, there is limited high quality evidence and long-term follow-up, identifying a lack of consistency, including a diversity of MSC preparations, and thus a lack of reproducibility amongst these articles' methods [9]. All of these reviews are positive with the safety of the cell therapy; however, there is still no sufficient evidence to show the efficacy. For those who want to know more details, please refer these papers. Here, we would like to review cell therapy of osteoarthritis from the points of cell sources, inclusion criteria and delivery methods applied in the clinical studies, and discuss the possibility to improve the clinical outcome by refining the clinical design.

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

Figure 1: Paper number on cell therapy for osteoarthritis from year 2000 to 2018, search results from PubMed with key words: ((Knee Osteoarthrosis) AND cell therapy).



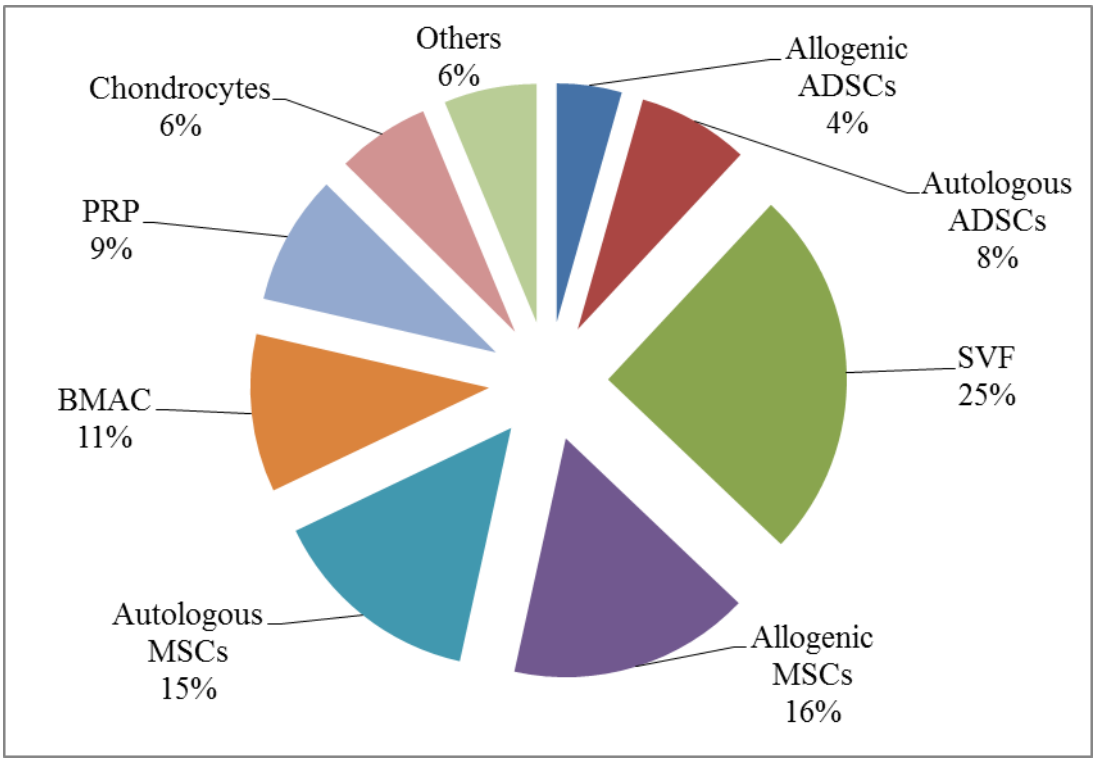
Current Status of Cell Therapy: cell sources, inclusion criteria and cell delivery methods

In order to see the detail of current clinical applications of cell therapy for OA, ClinicalTrials.gov (https://www.clinicaltrials.gov/ct2/search/advanced) search function was used to document all clinical trials registered (condition or disease: osteoarthritis, other terms: cell therapy, all other boxes in defaults). 180 clinical trials were registered on December 5, 2019.We analyzed the cell sources, inclusion criteria, and cell delivery methods of these clinical studies. The cell sources used in treatment of osteoarthritis are showed in Figure 2. Bone marrow and adipose are two major sources, accounted for 42% and 37%, respectively, following by PRP (9%) and autologous chondrocytes (6%). Cultured MSCs (from both bone marrow and adipose tissue) accounted for 43% while concentrated cell fractions (SVF&BMAC) accounted for 36%. The percentage of autologous MSCs (23%) is similar to allogenic MSCs (26%), indicating that the immune tolerance of MSCs were recognized and became acceptable. The components between concentrated cell fractions, such as BMAC [12] and SVF [13], and cultured MSCs [14] are totally different, which might result in different clinical results. Therefore, we need carefully to compare the results with different cell sources. Yokota et al. reported the comparative clinical outcomes with ADSCs or SVF for treatment of knee osteoarthritis, and showed that that both ASCs and SVF resulted in clinical

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

improvement in patients with knee OA, but that ADSCs outperform SVF in the early reduction of symptoms and pain with less comorbidity [15] (Figure 2).

Figure 2: Cell sources used in the cell therapy for osteoarthritis, search results from ClinicalTrials.gov on December 5, 2019 with key words: osteoarthritis and cell therapy.



Overall the inclusion criteria of cell therapy for osteoarthritis are broad. Typically, inclusion criteria are ages 40-70 years, OA with Kellgren-Lawrence grade over 2. There is no limitation on Hip-knee-ankle alignment, which influences load distribution at the knee, varus and valgus alignment increase medial and lateral load, respectively [16].It is reasonable to assume that if the alignment is not in acceptable range, for example malalignment <5 degrees, the load distribution will eventually affect the joint, and the effect of cell therapy would not last long. On this aspect, inclusion criteria of autologous chondrocytes implantation (ACI) is stricter, it clearly excluded those malalignment >5 degrees measured on HKA (hip-knee-ankle) radiographs [17]. To keep the efficacy of cell therapy for long-term, some limitation on alignment need to be considered. Almost all of the clinical studies of cell therapy forosteoarthritis delivered cell with intra-articular injection. This delivery method is simple, but it couldn't control and fix the cells to the target sites, such as cartilage lesion, as cells will distribute throughout the joint space after injections. It was reported the injected cell MSCs engrafted to synovial tissue, instead of homing to cartilage injury in normal or OA joints [18]. This suggests that the mechanisms of cell therapy with intra-articular injection may be

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

through modulation of synovial fluid constituents, inflammation, or cytokine profile, rather than direct cartilage repair. If this is true, this meant the cell therapy might be just a short-term improvement the symptom of joint, as it might not be able to repair the destroyed cartilage tissue. It was reported that change of subchondral bone might result in osteoarthritis [19]; treatment strategy of OA focused on subchondral bone might be required. Therefore, delivery of cells to subchondral bone might be another choice. Philippe Hernigou et al. reported subchondral injection of bone marrow cells can improve cartilage and bone marrow lesions [20].

Discussion

What is the goal of cell therapy? Because current therapy included diversity of cell sources, ambiguity of inclusion criteria, and simplicity of delivery methods, it reasonable to say each clinical study is different. As mentioned above, the components of MSCs, SVF, BMAC are totally different, which might result in different mechanisms to treat OA, and eventually resulted in different clinical outcome. So, when we perform a clinical study with cell therapy for OA, we need first to think what is the goal of the cell therapy? It is for pain relief, cartilage repair, or improvement of whole joint environment? How long we expect the treatment to last? To answer these questions, we need more preclinical studies in vitro and in vivo to characterize these cell sources and the action mechanisms. Based on the goal and the characteristics of each cell source, we can have more clear inclusion criteria and design specific clinical study to address the efficacy of the cell therapy. For example, for treatment of patients over 80-yearold's in a less invasive way, we might recruit patients over 80-yearold'sand treated them with SVF with intra-articular injections. On the other hand, if we want to pursue longer efficacy of this treatment and delay or substitute the TKA surgery, we might recruit patients under 60-yearold's, and treat them with MSCs by injection cells to subchondral bone.

Rehabilitation after cell therapy is not mentioned in these clinical studies, even though it is crucial to the biologic remodeling of the repair tissues [21]. Due to its importance, recently new field "regenerative rehabilitation" is proposed [21]. In this aspect, ACI has some concrete rehabilitation program [22], which might be useful for the other cells to refer. The ACI rehabilitation program divided into proliferation phase (first 4 to 6 weeks), transition stage (weeks 4-6 through week 12), remodeling phase (months 3-6), and maturation phase (lasts for up to 2 to 3 years). Each phase is designed based on requirement of the injected cells performance in vivo. In proliferation phase, the injected cell adhesion, proliferation and production of specific matrix markers to fill the defect. At this stage, supplement of nutrition to the implanted chondrocytes while avoiding the shear forces is important. As joint mobilization and partial loading is vital for the nutrition of the chondrocytes, passive ROM exercises should, therefore, postoperatively start as soon as tolerated, usually on day 1. In the

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

transition stage, the repair tissue has a spongy consistency and increasing lygains strength, the rehabilitation protocol will be focused on the restoration of full ROM, step-wise increase in weightbearing, and gait rehabilitation. In the remodeling phase, an increasingly organized structure of the tissue is formed, the focus of the rehabilitation program shifts to muscle strengthening and endurance as well as the return to functional training. In the maturation phase, matrix proteins stabilize in large aggregates and the collagen framework integrates in the subchondral bone. Rehabilitation concentrates on the restoration of full preoperative skills and the return to sports.

Although the effect of rehabilitation in cell therapy for OA is unclear, it has demonstrated that rehabilitation is a significant effect modifier of better ACI, facilitates the process of graft maturation, and allows a faster return to sports [23]. Integration of rehabilitation into cell therapy for OA might benefit in improving physical function, and improve the quality of clinical studies.

Disclaimer

The author has no any conflict of interest related to this article. The findings and conclusions in this paper are those of the author and do not represent the views of Olympus Corporation.

References

1. *https://www.who.int/chp/topics/rheumatic/en/*
2. *Bitton R.The economic burden of osteoarthritis.Am J Manag Care. 2009;15(8:230-5.*
3. *Liu Q, Wang S, Lin J, Zhang Y. The burden for knee osteoarthritis among Chinese elderly: estimatesfrom a nationally representative study.Osteoarthritis and Cartilage 2018;26(12):1636-42*
4. *https://www.oarsi.org/patients*
5. *Kellgren JH, Lawrence Js. Radiological assessment of osteoarthrosis.Ann Rheum Dis. 1957;16:494-502.*
6. *Jack M. Bert et al. The Conservative treatment of osteoarthritis of the knee. Orthopedics. 2018;41(5):256-60.*
7. *Hui C, Salmon LJ, Kok A, Williams HA, Hockers N, van der Tempel WM, et al. Long-term survival of High Tibial Osteotomy for medial compartment osteoarthritis of the knee.Am J Sports Med. 2011;39(1):64-70.*
8. *Steinhaus ME, Christ AB, Cross MB. Total Knee Arthroplasty for knee osteoarthritis: support for a foregone conclusion?HSS J. 2017;13(2):207-10*
9. *Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES.Osteoarthritis and stem cell therapy in humans: a systematic review. Osteoarthritis and Cartilage. 2018;26(6):711-29*
10. *Freitag J.Mesenchymal stem cell therapy in the treatment of osteoarthritis: reparative pathways, safety and efficacy - a review.BMC Musculoskelet Disord. 2016;26:17:230.*
11. *Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH1..Stem cell injections in knee osteoarthritis: a systematic review of the literature. Br J SportsMed. 2017;51(15):1125-33.*
12. *H Sugaya et al. Comparative analysis of cellular and growth factor components in Bone marrow Aspirate Concentrate and Platelet-Rich Plasma. Bone Marrow Res. 2018;25:1549826.*
13. *Lin K, Matsubara Y, Masuda Y, Togashi K, Tamura T. Characterization of adipose tissue-derived cells isolated with the Celution system. Cytotherapy. 2008;10(4):417-26.*
14. *Lee RH, Kim B, Choi I, Kim H, Choi HS, Suh K, et al. Characterization and expression analysis of mesenchymal stem cells from human bone marrow and adipose tissue.Cell PhysiolBiochem. 2004;14(4-*

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015

6):311-24.

15. *Yokota N, Hattori M, Ohtsuru T, Otsuji M, Lyman S, Shimomura K, et al.Comparative clinical outcomes after Intra-articular injection with Adipose-Derived Cultured Stem Cells or Noncultured Stromal Vascular Fraction for the treatment of knee osteoarthritis. Am J Sports Med. 2019; 47(11):2577-83*
16. *Sharma L, Song J, Felson DT,Cahue S, Shamiyeh E, Dunlop DD.The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286(2):188-95.*
17. *https://clinicaltrials.gov/ct2/show/NCT0041470*
18. *Watts AE, Noxon AJ. Distribution and homing of stem cells after intra-articular injection to normal and arthritic joints, Poster No. 1558, ORS 2012.*
19. *H L Stewart, Kawcak CE.The Importance of subchondral bone in the pathophysiology ofosteoarthritis. Front Vet Sci. 2018;5(178):1-9*
20. *Hernigou P, Auregan JC, Dubory A, Flouzat-Lachaniette CH, Chevallier N, RouardH.Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee.Int Orthop. 2018;42(11):2563-71.*
21. *HIijima,Isho T, Kuroki H, Takahashi M.Effectiveness of mesenchymal stem cells for treating patientswith knee osteoarthritis: a meta-analysis toward theestablishment of effective regenerative rehabilitation. NPJ Regen Med. 2018;3(15):1-13.*
22. *Hirschmüller A, Baur H, Braun S, Kreuz PC. SüdkampNP, Niemeyer P. Rehabilitation after autologous chondrocyte implantation for isolated cartilage defects of the knee.Am J Sports Med. 2011; 39(12):2686-96.*
23. *Della Villa S, Kon E, Filardo G, Ricci M. Does intensive rehabilitation permit early return to sport without compromising the clinical outcome after arthroscopic autologous chondrocyte implantation in highly competitive athletes?Am J Sports Med. 2010;38(1):68-77.*

Citation: Lin K. Short Review on the Advancement of Osteoarthritis Treatment with Cell Therapy. J Regen Biol Med. 2020;2(1):1-7.
This article has been published under Special Issue entitled: "Current concepts in orthobiologic solutions for osteoarthritis treatment". Edited by: *Dr. Gordon Slater*
DOI:https://doi.org/10.37191/Mapsci-2582-385X-2(1)-015