Editorial Commentary

Outcome of safety and efficacy of allogeneic mesenchymal stromal cell derived from umbilical cord for the treatment of osteoarthritis in a randomized blinded placebo-controlled trial

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Mesenchymal stromal cells (MSCs) have been attributed with many regenerative potentials such as ability to differentiate into a number of tissues such as bone, fat, cartilage and muscle, release wide range of growth factors and useful cytokines. These cells can be isolated from a number of tissue sources including bone marrow, adipose tissue, dental pulp, cord blood and umbilical cord. MSCs are heterogeneous, display plasticity, the Mesenchymal Stem Cell Committee of the International Society for Cellular Therapy (ISCT) has proposed three minimal criteria to define human MSC; they must be plastic adherent in tissue culture flasks that are maintained in standard culture conditions; over 95% of the cell population must express CD105, CD73 and CD90 and lack expression (≤2%) of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA class II; and must be able to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* under standard differentiating conditions (1).

Importantly, MSCs display immunomodulatory properties; modulate inflammation by releasing anti-inflammatory molecules in the injured or diseased sites in the body (2,3). These cells also have remarkable ability to suppress immune response and avoid immune rejection in tissue mismatched recipient, making it ideal for allogeneic treatment (3). Due to these therapeutic benefits, currently these cells are being explored for therapy in over 400 trials, preclinical and clinical trials around the world (4). One such condition for which the tissue regenerative properties of MSCs are being explored is for the treatment of osteoarthritis (OA). OA is a progressive degenerative disease in weight bearing joints such as the knee and is one of the most common chronic health problems that cause disability and chronic pain with reduced mobility in the world (5). The pathology of OA includes loss of cartilage volume and cartilage lesions leading to inflammation of the articular joint structures, and currently there in an unmet clinical need to treat this debilitating condition causing disability. In the current issue, Matas *et al.* (6) investigated the use of allogeneic Umbilical Cord-Derived MSCs for knee Osteoarthritis.

Allogeneic mesenchymal stromal cells provide a real possibility to treat osteoarthritis with no safety concern and especially no alloantigen reactivity in recipients, as shown by Matas *et al.* (6). This study is a well-designed randomized blinded placebo-controlled trial. The strong point of the study was the extensive testing carried out on both the recipient patients for humoral antibody detection, and the UC-derived mesenchymal stromal cells (UC-MSCs). A total of 29 patients in three cohorts (1:1:1); patients in controlled group that received a conventional injection of hyaluronic acid, cohort 2 received 1 injection of 40 million injection at 0 month and 3 mL of placebo (normal saline

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with 5% AB serum) at 6 month, and a third cohort receiving 2 injections of 40 million at 0 and 6 months with follow up assessment for safety and efficacy at week 1, 4, 8, 12, 24, 36, and 52 weeks. However, there are few limitations to this approach, firstly there are only 9 patients in each group which is a smaller number to draw any plausible conclusion on efficacy, secondly the follow up should be longer than a year to see any benefits was sustained over a long period of time of >2 years and finally the rationale behind only one selected dose of 40 million cells is not sufficient to justify the safety and efficacy of a new treatment.

Osteoarthritis Research Society International (OARSI) criteria for the evaluation of the effects of the treatment groups versus placebo and control group (7), to rule out the placebo effects was notable at 100% suggesting the clinical efficacy demonstrated was beyond the placebo effect (6). Based on the standard method for OA assessment, WOMAC (Western Ontario and Mc Master Universities Arthritis Index) and VAS (Visual Analog Scale) pain scoring system, the study reported at 12 month, patients in cohort 3 (group receiving two injections of MSCs) experienced 86% pain reduction and 89% disability reduction (P=0.001) contrasting to 38% and 50% in the control group that received HA, respectively. This result is very significant in terms of the osteoarthritis symptom management, as no other treatment is currently available to showcase such remarkable clinical benefits. Safety was also achieved with no severe adverse events in the treatment groups but moderate adverse events in few patients with acute synovitis that got resolved within one week with rest and with general analgesic. There was no detection of alloantigen as humoral immune response in the treatment groups that confirms the safety of allogeneic MSCs in the recipients. However, no improvement reported for structural changes for the OA knee in this study. This will require more optimal higher dosing regimen, as demonstrated by Jo *et al.* (8).

In a similar RCT evaluating autologous adipose derived MSCs for OA; 12-month outcome data reported recently (9), results exhibited similar improvement in pain and function from the baseline. Other similar studies have described the safety and efficacy of MSCs to treat OA successfully in autologous settings and with different tissue source of MSCs and a meta-analysis of screening 659 studies, of which 35 qualified studies (2,385 patients) suggested that MSC treatment for OA significantly improved knee pain (8,10-12). However, autologous cell therapy comes with its own limitations such as invasive surgery, limitation with the cost and the longer time frame as compared to the allogeneic "off the shelf" MSCs. The safety concerns for alloreactivity in recipients are addressed in the study by Matas *et al.* (6), with no evidence of unwanted immune response, no tumor formation and host rejection. The benefit of allogenic cell therapy provides other added advantages such as quicker accessibility, lower cost, well characterized and potency tested cells amongst other supply chain advantages.

UC-MSCs have been extensively investigated for their therapeutic benefits for a number of clinical conditions such as cardiomyopathy, motor neuron disease, diabetes, in the literature and are reported to be have rapider self-renewal, the potencies to differentiate into a variety of cells of three germ layers including bone, cartilage, cardiomyocyte, endothelium, hepatocyte-like cluster, islet-like cluster, neuron, and astrocyte, ability to secret useful trophic factors and cytokines., ability to home to diseased tissue sites (13). However, a comparative study of bone marrow, adipose tissues and umbilical cord derived MSCs showed no significant differences concerning the quality of the cells regarding their morphology and immune phenotype, colony frequency, expansion potential, multiple differentiation capacity, and immune phenotype (14).

In conclusion, as shown by Matas *et al.*, allogeneic MSCs therapy may provide efficacious therapeutic benefit for OA patients in mild OA. Allogeneic trials, similar to the autologous MSCs, have shown improved pain and function without serious adverse events in patients, however, more research is required. The treatment should be explored in severe OA patients with OA grade of 3 or more and also dose escalation study is warranted to examine any disease modifying effects such as structural modifications to halt OA progression in these patients. Future research should focus on a larger scale study with long term follow up to warrant making this innovative therapy mainstream for the wider OA patient population.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315-7.
2. Caplan AI, Correa D. The MSC: an injury drugstore. Cell Stem Cell 2011;9:11-5.
3. English K, Mahon BP. Allogeneic mesenchymal stem cells: agents of immune modulation. J Cell Biochem 2011;112:1963-8.
4. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. Cell Stem Cell 2015;17:11-22.
5. Shah K, Zhao AG, Sumer H. New Approaches to Treat Osteoarthritis with Mesenchymal Stem Cells. Stem Cells Int 2018;2018:5373294.
6. Matas J, Orrego M, Amenabar D, et al. Umbilical cord-derived mesenchymal stromal cells (MSCs) for knee osteoarthritis: repeated MSC dosing is superior to a single MSC dose and to hyaluronic acid in a controlled randomized phase I/II trial. Stem Cells Transl Med 2019;8:215-24.
7. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12:389-99.
8. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 2014;32:1254-66.
9. Freitag J, Bates D, Wickham J, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regen Med 2019;14:213-30.
10. Iijima H, Isho T, Kuroki H, et al. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. NPJ Regen Med 2018;3:15.
11. Orozco L, Munar A, Soler R, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: two-year follow-up results. Transplantation 2014;97:e66-8.
12. Pers YM, Rackwitz L, Ferreira R, et al. Adipose Mesenchymal Stromal Cell-Based Therapy for Severe Osteoarthritis of the Knee: A Phase I Dose-Escalation Trial. Stem Cells Transl Med 2016;5:847-56.
13. Fan CG, Zhang QJ, Zhou JR. Therapeutic potentials of mesenchymal stem cells derived from human umbilical cord. Stem Cell Rev 2011;7:195-207.
14. Kern S, Eichler H, Stoeve J, et al. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells 2006;24:1294-301.

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