Commentary: Cell-free Stem Cell-Derived Extract Formulation for Treatment of Knee Osteoarthritis
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Osteoarthritis (OA) is the most pervasive joint disorder impacting over millions of people each year. OA normally affects larger weight-bearing joints, with knees being most prevalent. It is anticipated to affect over 67 million people by 2030. Pathophysiology of OA is correlated with inflammation and decrease in vascularization in the articular cartilage degeneration. This leads to considerable pain and diminished function. Conventionally, OA is managed with immobilization, physical therapy, activity modification, pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs), and surgical interventions after traditional therapies have been futile. These treatment modalities have deficiencies, often attempting to lessen pain instead of aiming on underlying pathology.

Over the last decade, a handful of molecular targets, such as, interleukin-1 (IL-1), transforming growth factor-β (TGF-β), matrix metalloproteinases (MMP), etc. have been recognized as mediators of OA. Even though few of these targets are encouraging, they may well generate therapies with high risk-to-benefit ratio. Thus, alternative safe and effective treatment modalities are required to address this unmet medical need.

Lately, there has been a significant surge in the use of biologics for regenerative medicine applications. Biologics at present utilized in clinical practice include platelet rich plasma (PRP), liposapirate, bone marrow concentrate, and perinatal allogenic tissues including umbilical cord tissue, umbilical cord-derived Wharton’s Jelly, cord blood, and amniotic tissue (amniotic membrane and fluid). The efficacy of these biologics is ascribed to the presence of stem cells, growth factors, cytokines and extracellular vesicles, including exosomes.

First-generation biologics, particularly whole stem cell products, have gained significant interest for clinical regenerative medicine applications and demonstrated potential therapeutic benefits. Despite this, they are not without shortcomings, including creating a dependable source with a stable phenotype, genetic instability and chromosomal aberrations, intravenous administration associated toxicities caused by the physical trapping of the cells in the microvasculature of lungs, rejection by the host, formation of ectopic tissue, and tumorigenicity. To address the limitations and harness the benefit of stem cells into a next generation biologics, it is vital to understand the mechanism of action of stem cells. The present literature posits that the mechanism of action for beneficial effects of stem cells does not arise from their ability to grow and differentiate.
but is attributed to the secretion of bioactive molecules including growth factors, cytokines and exosomes. As the current literature further demonstrates that these bioactive components of stem cells generate definite regenerative responses, we have accordingly pursued to establish whether a sub-cellular method to biologics can deliver similar benefits while circumventing the risk profile associated with whole stem cells. Endorsing this hypothesis, current studies have shown that stem cells-derived exosomes can act as a cell-free therapeutic substitute to whole cell therapy with excellent regenerative potential. In addition to the advantages by means of risk removal, there may be additional therapeutic benefits of a cell-derived therapeutic methodology. For example, exosomes, given their smaller size, have the possibility to migrate to target organs efficiently, without getting trapped in the lung microvasculature. Furthermore, a greater concentration of “active ingredients” can be dispensed directly to the patient, which may stimulate a better healing response than likely with whole stem cell treatments.

To meet the objectives of improving the risk profile and beneficial effects of regenerative medicine, our group formulated a novel cell-free stem cell-derived extract (CCM) from human progenitor endothelial stem cells (hPESCs). Our published preliminary study showed the presence of numerous growth factors, anti-inflammatory cytokines and extracellular vesicles including exosomes in this formulation. This formulation, functionally, also substantially improved cell proliferation and stimulated stem cell migration. From this study, we concluded that the presence of multiple factors within one formulation along with its ability to increase the rate of cell proliferation and migration, may have the potential in reducing inflammation and pain and enhancing tissue repair and regeneration. In addition to our study, several peer-reviewed published studies via in vitro and preclinical work also demonstrated the potential of exosomes (i.e., cell free therapies) in treating knee OA. Despite this, there are no high level, peer-reviewed published clinical studies demonstrating the safety and efficacy of cell-free extract or exosomes for treatment of patients suffering with knee OA. To overcome this, we proposed a clinical trial to evaluate the safety and efficacy of intraarticular injection of our novel cell-free stem cell-derived extract formulation for management of knee OA (Kellgren-Lawrence Grade 2 or 3 knee OA). We anticipate that the intraarticular injection of our formulation is safe, and patients will demonstrate improvement in pain, function, quality of life and overall satisfaction. We also anticipate that cartilage formation will improve over a period of 2 years compared to the baseline. In addition to our trial, as of March 03, 2022, there is only one more ongoing clinical trial registered on ClinicalTrials.gov for knee OA related to Cell-free extract or exosomes. Both trials are summarized in Table 1. In summary, positive outcomes from our proposed clinical trial (NCT04971798) will lay the foundation for essential, prospective, larger, double-blinded, randomized controlled trials to further establish the safety and efficacy of our formulation to mitigate symptoms of knee OA, thereby, ultimately justifying its clinical use.

Table 1: Clinical trials registered on ClinicalTrials.gov till March 03, 2022 utilizing cell-free extract or exosomes for treatment of knee Osteoarthritis.

| Study Identifier | Tissue Type | Study Phase; Estimated Enrollment (N) | Primary Outcome Measure(s) | Recruitment Status | Country |
|------------------|-------------|--------------------------------------|----------------------------|--------------------|---------|
| NCT04971798      | human progenitor endothelial stem cells-derived extract formulation | Early Phase I; N=12 | Treatment-emergent adverse effects as assessed by Comprehensive Metabolic Profile; Creatinine Levels; Liver Function Test; Complete Blood Count; C-Reactive Protein; Erythrocyte Sedimentation Rate; T, B and NK Cell Lymphocyte Subset; Serum IgG, IgA, IgM and IgE levels [Time Frame: 1 week, 6 weeks, 3 months, 6 months, 12 months]: To determine safety i.e., adverse events associated with intraarticular administration of CCM as assessed by Comprehensive Metabolic Profile; Creatinine Levels; Liver Function Test; Complete Blood Count; C-Reactive Protein; Erythrocyte Sedimentation Rate; T, B and NK Cell Lymphocyte Subset; Serum IgG, IgA, IgM and IgE levels | Not yet recruiting | USA |
| NCT05060107      | Allogenic mesenchymal stromal cells-derived exosomes | Phase I; N=10 | Adverse Event [Time Frame: 12 months]: Occurrence of any adverse reaction within 12 months of treatment. | Not yet recruiting | Chile |
References

1. Main BJ, Maffulli N, Valk JA, et al. Umbilical Cord-Derived Wharton's Jelly for Regenerative Medicine Applications: A Systematic Review. Pharmaceuticals (Basel). 2021; 14(11): 1090.

2. Gupta A, Rodriguez HC, Potty AG, et al. Treatment of Knee Osteoarthritis with Intraarticular Umbilical Cord-Derived Wharton's Jelly: A Case Report. Pharmaceuticals (Basel). 2021; 14(9): 883.

3. Gupta A, Maffulli N, Rodriguez HC, et al. Safety and efficacy of umbilical cord-derived Wharton’s jelly compared to hyaluronic acid and saline for knee osteoarthritis: study protocol for a randomized, controlled, single-blind, multi-center trial. J Orthop Surg Res. 2021; 16(1): 352.

4. Gupta A, Maffulli N, Rodriguez HC, et al. Umbilical cord-derived Wharton's jelly for treatment of knee osteoarthritis: study protocol for a non-randomized, open-label, multi-center trial. J Orthop Surg Res. 2021; 16(1): 143.

5. Main BJ, Valk JA, Maffulli N, et al. Umbilical cord-derived Wharton's jelly for regenerative medicine applications in orthopedic surgery: a systematic review protocol. J Orthop Surg Res. 2020; 15(1): 527.

6. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. 2016; 29(6): 443-50.

7. Navani A, Manchikanti L, Albers SL, et al. Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2019; 22(15): S1-S74.

8. Gupta A, El-Amin III SF, Levy HJ, et al. Umbilical cord-derived Wharton's jelly for regenerative medicine applications. J Orthop Surg Res. 2020; 15(1): 49.

9. Gupta A, Cady C, Fauser AM, et al. Cell-free Stem Cell-Derived Extract Formulation for Regenerative Medicine Applications. Int J Mol Sci 2020; 21(24): 9364.

10. Matei AC, Antounians L, Zani A. Extracellular vesicles as a potential therapy for neonatal conditions: state of the art and challenges in clinical translation. Pharmaceuticals. 2019; 11(8): 404.

11. Bagno L, Hatzistergos KE, Balkan W, et al. Mesenchymal stem cell-based therapy for cardiovascular disease: progress and challenges. Mol Ther. 2018; 26(7): 1610-23.

12. Lau G, Chen Z, Zheng M, et al. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. Exp Mol Med. 2017; 49(6): e346.

13. Liew LC, Katsuda T, Gailhouste L, et al. Mesenchymal stem cell-derived extracellular vesicles: a glimmer of hope in treating Alzheimer's disease. Int Immunol. 2017; 29(1): 11-9.

14. Borger V, Bremer M, Ferrer-Tur R, et al. Mesenchymal stem/stromal cell-derived extracellular vesicles and their potential as novel immunomodulatory therapeutic agents. Int J Mol Sci. 2017; 18(7): 1450.

15. Maehara M, Toyoda E, Takahasi T, et al. Potential of Exosomes for Diagnosis and Treatment of Joint Disease: Towards a Point-of-Care Therapy for Osteoarthritis of the Knee. Int J Mol Sci. 2021; 22(5): 2666.

16. Li D, Gupta P, Sgaglione NA, et al. Exosomes Derived from Non-Classic Sources for Treatment of Post-Traumatic Osteoarthritis and Cartilage Injury of the Knee: In Vivo Review. J Clin Med. 2021; 10(9): 2001.

17. Jin Y, Xu M, Zhu H, et al. Therapeutic effects of bone marrow mesenchymal stem cells-derived exosomes on osteoarthritis. J Cell Mol Med. 2021; 25(19): 9281-9294.

18. Gupta A, Maffulli N, Rodriguez HC, et al. Cell-free stem cell-derived extract formulation for treatment of knee osteoarthritis: study protocol for a preliminary non-randomized, open-label, multi-center feasibility and safety study. J Orthop Surg Res. 2021; 16(1): 514.