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Stem Cell Therapy for the Treatment of Musculoskeletal Diseases: Safe and Effective or Costly and Temporary?

P. Hollands[1], D. Porter[2]

[1]Freelance Consultant Clinical Scientist, Cambridge, UK
[2]Medical Director, Opus Biological, London, UK

Corresponding Author: Peter Hollands, PhD; e-mail: peterh63@hotmail.com

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Abstract

This opinion paper reviews the use of expanded bone marrow mesenchymal stem cells (MSCs) in the treatment of musculoskeletal diseases, especially osteoarthritis and traumatic joint damage. This paper assesses past and present stem cell-based technologies, possible concerns about safety and efficacy, alternative or possibly parallel therapies using platelet rich plasma (PRP) and exosomes, as well as the latest concepts in modulated laser activation of stem cells. The clinical trial status and medical literature on this subject are considered, and the latest Good Manufacturing Practice (GMP) bioreactor technology is proposed as the gold standard for MSC expansion.

Regenerative medicine technology using a wide range of stem cells to treat an even wider range of diseases has been proposed over recent years[1]. There are many clinical trials underway to assess the safety and efficacy of these cell-based treatments, but the results are often confounding or driven by commercial rather than clinical decision making[2]. This has resulted in the provision of many stem cell-based therapies for profit by a wide range of private clinics across the world without underlying clinical trial data[3]. This situation results in many unanswered questions regarding the safety and efficacy of some stem cell-based therapies[4] and is of great concern to those who practice regenerative medicine in a safe and effective way with due regard for medical ethics and duty of care[5]. It is also essential that all cell-based therapies are regulated by competent authorities such as the UK Human Tissue Authority (HTA) and the Medicines and Healthcare products Regulatory Agency (MHRA) to ensure the safety and efficacy of any stem cell-based treatment[6].

The potential of mesenchymal stem cells (MSCs) - or mesenchymal stromal cells as some researchers prefer - as a means to reduce inflammation or to repair connective tissue is a clear paradigm in regenerative medicine[7]. This means that MSCs are an obvious candidate as a potential treatment for inflammatory and osteodegenerative diseases such as osteoarthritis[8] and traumatic joint damage[9]. The benefit-to-cost ratio of stem cell-based regenerative therapies in the treatment of osteoarthritis and related diseases has been highlighted recently. This is an area where all practitioners must ensure that any treatment offered is not only cost-effective but also clinically effective with ongoing benefits to the patient[10].

Many researchers advocate the use of autologous platelet rich plasma (PRP) in the treatment of musculoskeletal diseases[11]. PRP is a concentration of naturally occurring growth factors and cytokines which is capable of reducing inflammation[12], but in the basic form PRP cannot achieve any stem cell-based long-term repair of tissue damage. PRP also contains pluripotent very small embryonic-like stem cells (VSELs), which are thought to be inactive in normal physiology[13]. It has recently been shown that human VSELs in PRP can be activated by exposure to modulated laser light[14]. Such

technology may allow the use of PRP not only as a short-term anti-inflammatory treatment but also as a potential tissue repair technology through the action of activated pluripotent VSELs.

Some researchers suggested that MSC-derived exosomes are a good treatment modality for musculoskeletal diseases[15]. The proposal to use exosomes in this context is interesting and deserves much further research, although at present it does not represent a fully validated clinical methodology because of great variation in the quality and quantity of exosomes produced by various processing techniques from various starting points[16]. It is also likely that adipose tissue is a good source of MSCs for the treatment of musculoskeletal diseases, with benefits seen in patients up to 6 months after treatment initiation[17]. This suggests that MSCs provide long-term benefits to patients, which is important in procedures that are both invasive and relatively expensive to carry out. The processing of adipose tissue to optimize the number of MSCs available is constantly being refined. The latest research suggests that the stromal vascular fraction (SVF) and extracellular matrix (ECM) (buffy coat) given together as the stromal vascular matrix (SVM) will optimize the clinical efficacy when using adipose tissue as the source of MSCs for therapy[18].

At the time of writing there were 8 clinical trials recruiting (2 phase I, 2 phase I/II, 2 phase II, 1 phase II/III and 1 phase III) and 7 completed clinical trials which assessed the use of MSCs in musculoskeletal diseases. These completed clinical trials have confirmed the safety of using MSCs to treat musculoskeletal diseases[19]. In addition to these ongoing and completed clinical trials, there are an increasing number of publications in the medical literature assessing the use of MSCs in musculoskeletal diseases[20]. These data support the initial safety and efficacy of using MSCs to treat musculoskeletal diseases and provide the perfect foundation for further clinical trials and clinical studies in a safe and effective atmosphere for all patients and clinical trial volunteers.

The current MSCs of choice for the treatment of musculoskeletal diseases is obtained by the expansion of MSCs in bone marrow to provide enough MSCs for an effective treatment[21]. Initially this process was carried out manually, but the time taken to expand MSCs, the labour time needed, and the quality and reproducibility of the expanded cells were far from optimum[22]. This made the clinical application of such cells difficult logistically; also, the cells were not produced according to GMP standards and therefore each batch had variable therapeutic potency. More recently bone marrow-derived MSC expansion has been carried out using various automated bioreactors[23], which allow the production of GMP-expanded bone marrow MSCs for clinical use much more quickly and to a much better quality than manual expansion methods. The improved quality of the expanded bone marrow MSC from bioreactors will help to ensure that the long-term benefits to the patient are optimized in terms of cost *vs.* benefit consideration[24]. The GMP bioreactors also provide a much better paradigm for the regulatory authorities who seek consistent quality and safety of all cell therapy products.

It is our opinion that the use of GMP bioreactors for the expansion of bone marrow MSCs is not only clinically safe and effective, but it offers a long-term cost-effective treatment strategy for musculoskeletal diseases. This is because the bioreactor expanded MSCs obtained are of the highest quality and safety and this is reproducible for every patient. Bioreactor-based stem cell expansion is the current gold standard[25] and it should be adopted by all those who seek to use expanded bone marrow MSCs for the treatment of musculoskeletal diseases. This is based on our own experience and also on data available from past and present clinical trials and medical literature[26]. New technology in the future[27] may change or revise this position, and an open mind on these matters is always critical to make progress and offer our patients safe, clinically effective and cost-effective stem cell-based therapies.

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ORCID:
Peter Hollands: https://orcid.org/0000-0003-4116-1954
David Porter: https://orcid.org/0000-0001-9659-0196

Conflict of Interest:
Peter Hollands is a freelance consultant clinical scientist and has no conflict of interest to disclose. David Porter is Medical Director of Opus Biological (London, UK).

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