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Treatment of Osteoarthritis with Autologous and Allogeneic Expanded Bone Marrow Mesenchymal Stem Cells

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

In this review we explore the past, present and future treatment of osteoarthritis using autologous and allogeneic bone marrow mesenchymal stem cells (MSCs). Osteoarthritis is one of the most prevalent joint diseases worldwide. It causes pain, loss of function and may lead to disability. At a cellular level, osteoarthritis causes biochemical changes in the composition of cartilage leading to progressive tissue degeneration. The majority of conventional treatments involve symptom control but offer only modest clinical benefits without any reversal of the cellular degeneration. Cell-based therapies in animal models have shown encouraging results and there are now a number of human case reports, pilot studies and follow-up studies that demonstrate the reversal of lesion formation. Opus Biological has designed a therapy and follow-up algorithm utilizing the feasibility and safety studies conducted in recent years to offer patients MSCs as a valid alternative to other conventional therapies for treatment of chronic osteoarthritis. MSC therapy for osteoarthritis does not require hospitalization, is a minimally invasive and low risk procedure, provides pain relief and significantly improves cartilage quality thereby enhancing joint function.

Introduction

Osteoarthritis (OA) is the most prevalent chronic joint disease as well as a frequent cause of joint pain, functional loss and disability[1,2]. The disease most commonly affects the joints of the knees[3], hands[4], feet[5] and spine[6]. It is also relatively common in shoulder[7] and hip joints[8]. Even though OA is most commonly related to aging[9], there are also a number of modifiable and non-modifiable risk factors for the development of this condition. These include obesity[10], lack of exercise[11], genetic predisposition[12], bone mineral density status[13], occupational injury[14], trauma[15] and female sex (due to menopause)[16]. Globally there is an estimated 10-15% prevalence of OA, with the numbers higher in the female population[17]. OA is an increasing risk to our global community due to the advances in medicine leading to an aging population and due to increases in the prevalence of modifiable risk factors such as obesity[18]. According to recent estimates, by 2050 the number of people aged over 60 will account for more than 20% of the world's population. By 2050, 130 million people will suffer from OA worldwide, and 40 million will be severely disabled by the disease. A World Health Organization report estimates that of 20% of those aged over 60, a conservative 15% will have symptomatic OA, and 33% of these people will be severely disabled by OA[19]. The cost to society of OA can be measured not only in the cost of adaptive aids and devices but also in the cost of medication, surgery[20], nursing care, residential care, and time off work and subsequent social care relating to sick

pay. International institutions have been reluctant to put a figure to the large indirect costs derived from the decrease in productivity caused by OA.

Pathogenesis of OA

Although there are still many unknowns in the pathogenesis of OA, this appears to be primarily linked to biochemical and biomechanical changes in the joint cartilage[21]. The current models suggest that suboptimal nutrient (glucose)[22] and oxygen supply[23], coupled with downregulation of extracellular/pericellular matrix components[24], increased supply of proteinases[25] and a relative increase in apoptosis of chondrocytes[26], accounts for a cumulative effect on the inability to withstand normal mechanical stresses. The resultant cartilage debris alongside catabolic mediators in the joint promote the activation of synovial macrophages[27], which in turn leads to synovial inflammation[28] that limits native cartilage repair[29].

Current Treatment of OA

The American Academy of Orthopaedic Surgeons recommends only physical[30] and educational therapy[31], symptomatic drugs such as paracetamol[32], non-steroidal anti-inflammatory drugs[33] and in some cases intra-articular corticosteroid injections[34]. The American College of Rheumatology recommends a similar regimen including physical therapy, viscosupplementation[35] with hyaluronate injections[36], and possible but conflicting evidence for glucosamine[37] and/or chondroitin sulphate[38]. Arthroscopic surgery[39] and acupuncture[40,41] have only demonstrated modest clinical benefits. Another alternative treatment modality investigated over recent years is Autologous Chondrocyte Implantation (ACI)[42]. Briefly, chondrocytes are taken from patients, culture-expanded *in vitro* and then re-implanted back into the affected joints of patients. The procedure is invasive and has been shown to be less successful than the total knee replacement surgery to date[43].

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs, sometimes also referred to as Mesenchymal Stromal Cells) [44,45] were identified in the 1970s while examining the clonogenic potential of bone marrow cells. MSCs were initially termed "colony-forming unit fibroblasts" (CFU-Fs)[46]. Clinical trials investigating the use of MSCs began in 1995, with the results demonstrating no adverse reaction and no safety concerns, and since then hundreds of clinical trials have followed[47]. In 2006, The International Society for Cellular Therapy (ISCT) published the criteria for defining MSCs[48]. The ISCT stated that MSCs must be plastic-adherent under standard *in vitro* culture conditions; express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a, CD19, and HLA-DR (as assessed by flow cytometry). In addition, the ISCT stated that MSCs must be able to differentiate into osteoblasts, adipocytes and chondrocytes *in vitro*[48]. MSCs have been shown to be present in bone marrow[49], umbilical cord blood (with an associated clinical trial to treat cerebral palsy)[50], umbilical cord tissue[51], placenta[52], amniotic membrane[53], amniotic fluid[54], periosteum[55], trabecular bone[56], adipose tissue[57], synovium[58], skeletal muscle[59] and deciduous and permanent teeth[60]. Independent of their origin, MSCs are capable of differentiating *in vitro* into different cell types of the connective tissue lineages such as bone, fat, muscle, tendon and ligament as well as cartilage[61]. MSCs have been shown to elicit immunosuppressive and immunomodulatory effects[62] on T lymphocytes[63], B cells[64], dendritic cells (DCs)[65] and natural killer (NK) cells[66]. These effects occur either via the cell-cell interaction route[67] or via the secretion of anti-inflammatory molecules such as indoleamine 2,3-dioxygenase (IDO)[68], prostaglandin E2 (PGE2)[69], interleukin-4 (IL-4)[70], interleukin-10 (IL-10)[71] and transforming growth factor beta (TGF-β)[72]. These properties make MSCs the ideal choice for cell-based regenerative medicine procedures[73]. The ability to differentiate *in vitro* into chondrocytes[74], combined with their anti-inflammatory and immunomodulatory properties, make MSCs the obvious choice for the treatment of diseases such as OA[75]. Autologous[76] or allogeneic[77] bone marrow-derived MSCs are the most widely used MSCs in clinical research and treatment modalities across a plethora of disease indications, and are often considered to be the gold standard MSC type[78] because of the characterization that has occurred exhaustively over the last 5 decades[79].

Over the last 25 years the surgical implantation of autologous chondrocytes has been used to treat

local cartilage defects[80]. MSCs have chondrogenic potential which is enhanced by co-culture with chondrocytes[81]. Co-cultured MSCs induce chondrocyte proliferation and extracellular matrix protein synthesis, including aggrecan[82] and type II collagen[83]. Therefore, MSCs can be used in place of chondrocytes for cartilage regeneration[84]. The replacement of chondrocytes with MSCs is advantageous especially for diffuse chondral lesions as MSCs are more readily obtainable and can be expanded *in vitro*[85]. A publication in 2010 argued on the merits of autologous bone marrow-derived MSCs *vs.* autologous chondrocyte implantation and observed that MSCs are as effective in cartilage repair as implanted chondrocytes. In addition, MSCs were more cost-effective, reduced donor site morbidity and resulted in one less knee surgery[86].

The philosophy of most current cell-based therapeutic approaches to the treatment of OA is to take the treatment to the site of the injury[87]. Intra-articular injection of cell-based treatments such Platelet-Rich Plasma (PRP)[88] or MSCs[89] allows these cells to interact with recipient cells and with the surface area within the joint space specifically targeting injured or degenerated tissues[90]. MSCs are regulated by the microenvironment which they inhabit and by the interactions with the surrounding cells[91], and they secrete bioactive factors for tissue regeneration in response to that microenvironment[92]. In the future it may also be possible to utilize the MSC-secretome to avoid the use of MSCs, thus potentially simplifying the treatment[93]. Nevertheless, it is likely that the MSCs themselves may have more actions than simply the secretome alone in the overall tissue repair process[94].

The immunomodulatory effects of MSCs have been described above, but it is worth reminding that MSCs have a multimodal mechanism of action making them the "cell candidate of choice" in the treatment of OA. This is because MSCs stimulate native chondrogenic progenitor cells and their subsequent differentiation into mature chondrocytes mediated by bone morphogenetic proteins (BMPs)[95] and TGF-β1[96]. The differentiation of the MSCs themselves into chondrogenic progenitor cells is mediated by changes in the expression of regulatory genes like *Sox9, HoxA, HoxD* and *Gli3*[97]. These chondrogenic progenitor cells then differentiate into mature chondrocytes with the ability to synthesize type II collagen, which maintains the structural integrity of hyaline cartilage[98].

Autologous Mesenchymal Stem Cells

Animal studies have shown beneficial effects on cartilage repair utilizing autologous MSCs in rabbits[99], rats[100], pigs[101] and guinea pigs[102]. The analgesic effect of MSC treatment in humans has been reported and this effect can be enhanced even further by the pre-treatment using the CB2 receptor agonist AM1241[103]. The use of human autologous expanded bone marrow MSCs has been demonstrated to be effective in the treatment of chronic patellar tendinopathy[104] and in degenerative disc disease[105,106].

We have safely conducted intra-articular infusions of $40x10^6$ autologous expanded bone marrow MSCs in patients with grade 2-4 OA of joints including the knee, hip, ankle, shoulder, and wrist. These treatments were carried out in the UK under a Medicines and Healthcare Products Regulatory Agency (MHRA) and a Human Tissue Authority (HTA) license. Expanded bone marrow MSCs are categorized to be Advanced therapy medicinal products (ATMPs)[107]. The current research is highlighting the efficacy of expanded MSCs[108] in both patient outcome and duration of effect[109]. The process of MSC expansion is, quite rightly, highly regulated and the MSCs generated are subject to rigorous quality and safety testing throughout manufacturing before they are released for treatment[110].

The patients underwent follow up at 3-, 6-, 12- and 24-month intervals with outcome scores for pain and function at each stage. Clinical examination was also performed at the same time as utilizing validated outcome tools. Prior to treatment our patients underwent Magnetic resonance imaging (MRI) of the affected joint and at 12 months had a repeat MRI scan to discern radiological improvements. The patients were assessed using quantitative T2 mapping[111] to evaluate articular cartilage quality as T2 relaxation time is sensitive to changes in cartilage hydration and collagen fibril orientation[112]. OA is known to cause an increase in T2 relaxation time[113]. T2 mapping and whole-organ magnetic resonance imaging score (WORMS)[114] are currently the most common qualitative parameters for evaluation of cartilage regeneration, although the optimal imaging study would be able to provide an accurate assessment of cartilage thickness and volume, show morphologic changes to the cartilage surface, demonstrate internal cartilage signal changes and determine signal abnormalities

in subchondral bone. Orozco et al[115] showed the safety and efficacy of autologous expanded bone marrow MSCs administered in 12 patients with chronic knee pain unresponsive to conservative treatments and radiologic evidence of OA. Quantification of cartilage quality by T2 relaxation measurements showed a highly significant reduction of poor cartilage areas, with improvement of cartilage quality in 11 of the 12 patients[115].

Autologous Expanded Bone Marrow-Derived MSC Treatment: The Procedure

The procedure in the UK must begin with a Human Tissue Authority (HTA) Human Application License for the procurement and distribution of human cells or tissues. The patient receives conscious sedation, in a hospital operating theatre with local anaesthetic, and 60-100 mL of bone marrow is collected from the posterior iliac crest of the patient. The aspirate is then transferred to the expansion laboratory via an approved medical courier if the laboratory is not on the same site as the procurement operating theatre.

MSC Isolation and Expansion

MSC isolation and expansion is typically performed in a laboratory under Good Manufacturing Practice (GMP) conditions and in the UK with license from the MHRA. The MSC expansion laboratory must also be licensed by the HTA UK for processing, storage and distribution of human cells and tissue for Human Application. MSC expansion is then carried out using either a manual technique[116] or by the use of a closed system bioreactor[117]. In either case the phenotype and potency of the resultant MSCs must be retained. The manual expansion technique is slow and labour-intensive, whereas the bioreactor technology enables more cells to be produced in less time with less manual labour.

The expanded MSC product is tested for sterility, Mycoplasma and endotoxin[118]. The results of the quality control testing, together with the full review of the batch documentation and the results of all environmental monitoring that took place during the cell culture process, allows the intermediate product to be released for use as the final product. The final product is transported, within temperature-controlled containers, by a dedicated medical courier service to the treatment center for administration to the patient.

Allogeneic MSCs

Initially, the use of allogeneic MSCs was limited due to the concern that they would lose their immunogenicity and immunomodulatory properties on transplantation[119]. MSCs do not express class II human leukocyte antigen (HLA) molecules[120] and are therefore considered to be immune privileged[120] or possibly "immune evasive"[121]. The proposed use of allogeneic MSCs for clinical purposes has resulted in recent increases in the number of studies exploring the possibility of using allogeneic MSCs for the treatment of cartilage injuries[122]. Allogeneic MSCs have been combined with isolated autologous chondrocytes in a fibrin glue and applied to focal areas of cartilage damage[123]. There have been no reported immunological issues from any of these studies. The use of allogeneic MSCs in the treatment of OA has demonstrated significant improvements in pain, leading to an overall improvement in joint function and suggesting cartilage regeneration on imaging[124]. The use of allogeneic MSCs has a number of benefits for the patient. Allogeneic MSC treatment is less expensive and less time-consuming than the autologous version. The utilization of allogeneic MSCs removes certain key steps in the process, such as admission to a hospital facility and then an operating theatre procedure for bone marrow aspiration under conscious sedation.

Conclusions

We have a team which is a collective of unique and experienced healthcare professionals working together with one unified vision to bring the state of the art of stem cell treatment to patients as a safe and effective option for those seeking an alternative avenue to conventional treatments. Stem cell science is not new, in fact the technology is decades old, but only now are scientists and clinicians harnessing and understanding the potential of this avenue for a broad spectrum of diseases. We have seen the power of MSCs throughout our own practice in the treatment of musculoskeletal injuries and diseases. We work with the academic community and the regulators in the UK and the EU to adhere to the core of scientific

principle and abide by regulations that preserve our patients' safety. Our world leading scientific laboratory can tailor the treatments that we offer to those suffering from musculoskeletal injury and disease. MSC-based therapy provides a complete package of care on the orthobiologics spectrum, from PRP through allogeneic to autologous MSCs. We understand that not all of our patients will require MSC treatment, but we also understand that patients want relief from pain of OA and a betterment in their daily lives. The spectrum of orthobiologics now available can help our patients to experience pain free function alongside a renewed sense of health. In the age of "one size fits all" practice we want to put the power back into the hands of our patients. We deliver truly unique and individualized care for each patient, in partnership with world class professionals. In the future we aim to help patients suffering from an array of conditions across a multitude of specialities ranging from those with Crohn's disease[125] to patients experiencing the life limiting consequences of multiple sclerosis[126]. Stem cell science can be the forefront of disease modification and, more importantly, disease reversal in such conditions.

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ORCID:

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

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Peter Hollands has no conflict of interest to disclose. David Porter is Medical Director of Opus Biological (London, UK).

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