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Narrative Review

Stem Cell Therapy for Chronic Pain Management: Review of Uses, Advances, and Adverse Effects

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Background: This review article outlines the recent advances, uses, and adverse effects of cell-based therapy for chronic pain management. Cell based therapies are gaining increasing ground as novel treatment modalities for a variety of pain pathologies that include, but are not limited to, neuropathic pain and degenerative disc disease. As these treatment modalities become more common practice, we have focused our review to provide pain practitioners and other practicing physicians an understanding of the technology and to summarize key clinical data and existing clinical trials that are being pursued by clinical investigators worldwide.

Objective: Review of stem cell technology and applications in pain management.

Study Design: Narrative review.

Methods: The Pubmed NCBI and EMBASE databases was utilized to review published reports of clinical studies reported from 2000 to 2015, and ClinicalTrials.gov (www.clinicaltrials.gov/ct2/search) search function was used to document ongoing clinical trials [keywords: "chronic pain," "disc pain," "cell therapy," "osteoarthritis," "neuropathic," "stem cell"] currently active and recruiting patients.

Results: Articles were screened by title, abstract, and full article review. They were then analyzed by specific clinical indications and appropriate data were presented based on critical analysis of those articles.

Limitations: More studies looking at the systematic use of stem cells in pain management will be required to draw conclusions about the benefits of the technology.

Conclusion: Though the data from existing studies look promising for the use of stem cells as a novel therapeutic strategy for discogenic pain, neuropathic pain, and osteoarthritis, additional clinical studies will be needed to validate the benefit of the technology for clinical use. However, we hope that this narrative review will help guide pain physicians in making informed decisions for their patients about the potential of cell-based therapy for treating chronic pain conditions.

Key words: Stem cell therapy, chronic pain, clinical trials, disc pain, neuropathic pain, mesenchymal stem cells, osteoarthritis, pain management

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At present, chronic pain affects 1.5 billion people worldwide, with 23 to 26 percent of the population experiencing lower back pain alone (1). Cell-based therapy is making critical advances in providing a novel approach to treating common chronic pain syndromes such as degenerative joint disease and neuropathy. It is a unique treatment modality that provides replacement of lost and

injured cells while also serving as a delivery vehicle for various trophic factors. Some stem cells are derived from human embryos or from tissues like the skin in the adult. Others can be created in a mature cell of the adult. In recent years, stem cell therapy has been a topic of great interest for health, disease, and biomedical research into regenerative medicine (2-5). For instance, hematologic conditions, burn therapy, bone grafting, and corneal transplants all exemplify current uses of stem cell therapy. In fact, stem cells have been used clinically since the 1960s in the form of bone marrow transplants to treat leukemia (6,7). Using stem cells can offer solutions for treating painful conditions such as bone and cartilage defects, osteoarthritis, tendon and ligament injuries, and maybe even nerve damage (8,9). Some clinics are even injecting stem cells into degenerative discs of the spine. Although it's too early for a definitive conclusion, stem cells may have the capacity to control not only the symptoms of chronic pain, but act to modify the disease itself.

Our objective in this review is to provide pain medicine specialists an overview of the current state of the literature regarding cell-based therapy. We discuss previously published reports and active clinical trials in this field to provide practitioners a guide for using stem cell therapy as an alternative to traditional therapies for controlling pain.

Mesenchymal stem cells (MSCs) have shown tremendous promise due to their easy availability and cell homing potential. MSCs are originally derived from the bone marrow. They possess 2 important properties: long-term self-renewal ability and the capacity to differentiate along multiple cell lineages. They can usually be grown using standard culture techniques to achieve osteogenic, chondrogenic, and adipogenic differentiation potential (10,11). Moreover, studies on both humans and animals have established the safety of autologous MSC administration (12-16).

Other sources of MSCs include adipose tissue that can serve as large reservoirs when compared to alternative sources such as bone marrow, skeletal muscle, and umbilical cord blood (10,11). The culture medium is especially important since differentiation of stem cells is dependent on the microenvironment, growth factors, and extracellular matrix. Furthermore, specific cytokines including TGF-β and bone morphogenic protein (BMP) can be important in promoting chondrogenesis and selective stem cell differentiation (10,11).

In recent years, considerable research efforts and funding have been tailored toward understanding the utility of MSCs for treating various pain pathologies. These studies have highlighted the benefits of this technology, but have counterbalanced their promise in some instances by acknowledging various complications such as tumor formation, undesirable bone formation, and abnormal immune reactions. At present, there is no systematic, clinically oriented review examining the merits of this technology for chronic pain management. We hope to present a clinically driven focus in this review of current studies and clinical trials to assess the safety, efficacy, and applicability of cell-based therapy for chronic pain conditions.

In this review, we will describe clinical studies of cell-based therapy for the treatment of several common chronic pain conditions: lower back pain, neuropathic pain, and osteoarthritis. Due to the therapeutic limitations of medical and surgical management, there has been significant interest in the development of cell-based therapies.

Methods

This was a focused review of the literature examining clinical trials for chronic pain syndromes related to the most commonly modeled syndromes: degenerative disc disease, osteoarthritis, and neuropathic and musculoskeletal pain. The Pubmed NCBI and EMBASE databases were accessed to review published reports of clinical studies reported from 2000 to 2015 using key words: "chronic pain," "disc pain," "cell therapy," "osteoarthritis," "neuropathic," "stem cell," "musculoskeletal," "tissue repair pain," and "cartilage stem cell," while prior reviews were also searched for pertinent original studies. Additionally, the ClinicalTrials.gov (www.clinicaltrials.gov/ct2/search) search function was used to document ongoing clinical trials (key words: "chronic pain," "disc pain," "cell therapy," "osteoarthritis," "neuropathic," "stem cell," and "musculoskeletal") currently active and recruiting patients.

Results

Discogenic Pain

The majority of clinical studies on chronic pain have focused on outcomes rather than pathophysiological mechanisms. Recently published studies in individuals with chronic pain syndromes are summarized in Table 1. In this review, we will first highlight reports of discogenic pain. Human MSCs have been the most commonly used in patients for the treatment of lower back pain. The nucleus pulposus contains MSCs that are

similar to the MSCs recovered from bone marrow; co-culturing of MSCs with nucleus pulposus cells stimulates both nucleus pulposus cell proliferation and MSC differentiation toward the chondrogenic lineage (17). Transplanted MSCs induce production of extracellular matrix proteins, proteoglycans including aggrecan, and types I and II collagen. Risbud et al (18) reported that in specific microenvironmental conditions, bone marrow mesenchymal stem cells (BM-MSCs) are able to differentiate into nucleus pulposus-like cells. Hypoxia and TGF-β were found to concurrently activate gene cassettes within the nucleus pulposus cells that encode for extracellular matrix and cell surface receptors. The study also noted that low oxygen tension and TGF-β1 can trigger ERK and p38 signaling pathways, ultimately promoting MSC differentiation. In a recent case report, Pang et al (16) described a greater or equal to 50% improvement in pain and functional scores up to 24 months in 2 patients injected with umbilical cord MSCs after discography. This reflects earlier findings which also suggested clinical benefit in small groups of patients who had received cell therapy. Orozco and colleagues (17) also reported encouraging findings from their study on 10 patients with back pain secondary to lumbar disc degeneration. For instance, after injections of autologous expanded (BMSCs) into the annulus fibrosis, patients experienced a mean decrease in lumbar pain from 68.9 to 20.0 on a 100-point scale at 12 months. Sciatic pain was reduced as well from a mean of 37.0 to 5.3 (also out of 100), while disability scores also decreased from a mean of 25.0 to 7.4 (out of 100). Yoshikawa and colleagues (19) reported decreases in pain score and increased signal intensity of intervertebral discs at a 2 year follow-up of 2 patients who received percutaneous lumbar grafts of MSC-containing collagen. However, preoperative pain scores were not recorded and degree of benefit cannot be verified. A more recent study by Mochida et al (20) used a different approach involving mesenchymal cell co-culture and implantation of autologous nucleus pulposis cells in patients with lumbar disc degeneration after spinal fusion. Nine patients between the ages of 20 and 29 were enrolled and received treatment; follow-up occurred intermittently from one week to 3 years. No adverse outcomes were reported, and patients showed an average improvement of 13 (out of 29) points in function and 1.5 (out of 3) in terms of lower back pain intensity at 3 years. Most recently, Pettine et al (21) divided 26 patients into 2 groups: one which received MSC injection at a single disc in the lumbar spine, and another which received MSC injections at 2 adjacent discs. Patients who received a single level injection ultimately reported a decrease in pain scores from 78.5 to 31.4/100 at 12 months, while patients who received bi-level injection reported a decrease from 79.4 to 33.0/100 at 12 months. Their disability scores (as measured by Oswestry Disability Index) decreased as well over this interval.

The largest study, conducted by Meisel and colleagues (22), reported an interim subset analysis of the multi-center EuroDISC trial. It involved the percutaneous injection of autologous disc-derived chondrocytes into the annulus of patients approximately 12 weeks after single-level discectomy (22). Unlike other studies, this was randomized and controlled. After 2 years, patients who received cell transplantation after microdiscectomy reported comparatively less pain and dysfunction compared to microdiscectomy alone. This study does contain important caveats. From a technical standpoint, the cells were harvested from sequestered disc fragments, raising the question of line viability. Moreover, they required processing that may not be available at all centers. The study was not blinded and there is the possibility for placebo effect. Finally, given that the cells were introduced percutaneously, it is difficult to verify whether they remain contained within the annulus fibrosus of the transplanted disc and whether the transplanted cells can survive in their novel environment. Additionally, the results of the EuroDISC trial reflect interim data; they appear promising but completed trial results (in terms of a full patient data set) have not yet been published. Although these and other data have highlighted beneficial results, not every study has proven successful. For instance, Haufe and Mork (23) reported that the intradiscal injection of hematopoetic precursor cells provided no benefit in a group of 10 patients aged 32 to 74 with lower back pain who had failed endoscopic discectomy. These patients also received hyperbaric oxygen therapy to boost disc perfusion. Unfortunately, none of the patients in the study reported improvements in their visual analog pain scores at one year follow-up. This particular study was also limited by no description of back pain etiology or pre- and post-procedural pain scores.

Overall, while some cell-based therapy studies for disc degeneration have yielded encouraging results without concerns for complications, more studies are required to address the generalizability of data. Many of the studies discussed above were not randomized, blinded, or controlled. Thus, it cannot be ascertained whether the therapeutic benefits derive from treat-

Table 1. *Clinical studies in patients with chronic pain.*

Study ID	Stem Cell Type	Disease	Study Design	Source	Number of Patients	Follow up period	Outcome	Comments
Discogenic Pain								
Pang et al (2014)	Mesenchymal Stem Cells (MSC)	Chronic back pain	Prospective, observational	Umbilical Cord MSC	2	2 years	Pain scores decreased from 7 to 1 and 8 to 4 at 2 years.	Small number of patients, study not controlled
Orozco et al (2011)	MSC	Chronic back pain	Prospective, observational	Bone Marrow MSC	10	1 year	Mean lumbar pain score decreased from 68.9 to 20.0/100 at 12 months; mean disability score decreased from 25.0 to 7.4 at 12 months.	Small number of patients, study not controlled
Yoshikawa et al (2010)	MSC	Disc degeneration	Prospective, observational	Bone Marrow MSC	2	2 years	Pain scores decreased to 38/100 in one patient and 18/100 in the other.	Small number of patients, study not controlled, preprocedural pain scores not documented.
Mochida et al (2015)	MSC	Disc degeneration	Prospective, observational	MSC co-cultured nucleus propulsus cells	9	3 year	Function scores improved from 14.2 to 27.2/29 at 3 years.	Small number of patients, study not controlled
Haufe & Mork (2006)	Hematopoetic Stem Cell (HSC)	Discogenic back pain	Prospective, observational	Bone marrow aspirate	10	1 year	No improvement in pain scores at 1 year.	Small number of patients, study not controlled
Pettine et al (2015)	Nonspecific	Discogenic back pain	Prospective, observational	Bone marrow concentrated cells	26	3 months through 1 year	In patients who received injections at 1 level, average pain score decreased from 56.5 to 26.2/100. In patients who received injections at 2 levels, pain score decreased from 55.5 to 22.7.	Study not controlled,
Meisel et al (2007)	Chondrocytes	Discogenic back pain	Prospective, randomized, controlled trial	Disc chondrocytes	28	2 years	Patients showed improvements in terms of pain and disability.	Interim analysis.
Neuropathic Pain								
Vickers et al (2014)	MSC	Trigeminal Neuralgia	Prospective, observational	Lipoaspirate MSC	10	6 months	Mean pain score decreased from 7.5 to 4.3 at 6 months.	Small number of patients, study not controlled.
Venturi et al (2015)	Adipose-derived stem cells (ASC)	Pudendal neuralgia	Prospective, observational	Autologous fat cells	15	7 days through 12 months	Mean pain score decreased from 8.1 to 3.2 at 12 months. Composite functionality scores improved.	3 patients did not follow up and 2 were excluded due to no improvement in pain. No control group.

Table 1 (cont.). *Clinical studies in patients with chronic pain.*

Study ID	Stem Cell Type	Disease	Study Design	Source	Number of Patients	Follow up period	Outcome	Comments
Degenerative Joint Disease								
Wakitani et al (2002)	MSC-gel composite versus collagen gel-sheet only	Knee osteoarthritis	Prospective, randomized, controlled trial	Bone marrow aspirate	24	14.3 months for cell transplant, 17.5 months for gel-only	Composite score as described in text improved from 65.0 to 81.3/100 for cell transplant patients, 66.3 to 79.2/100 for gel-only patients.	No significant difference in the relative clinical improvement between groups. Improved histological findings in terms of cartilage regeneration in cell transplant patients on following operations.
Centeno et al (2008)	MSC	Knee osteoarthritis	Prospective, observational	Bone marrow aspirate	1	4 through 24 weeks	Patient's pain score decreased from 4 to 0.38/10 at 24 weeks.	Single case study.
Centeno et al (2011)	MSC	Multiple joint conditions	Prospective, observational	Bone marrow aspirate	339	Mean 435 days	Outcomes for knee joint patients reported - 41.4% of patients reported greater than 75% improvement in symptoms.	2 cases of cancer in patients who received therapy.
Emadedin et al (2012)	MSC	Knee osteoarthritis	Prospective, observational	Bone marrow aspirate	6	2 weeks through 1 year	Mean pain score decreased from 57/100 to 11.6/100 at 12 months. Function improved and walking distance increased.	Small number of patients, study not controlled
Emadedin et al (2015)	MSC	Multiple joint conditions	Prospective, observational	Bone marrow aspirate	18	2 through 30 months	Decreased pain scores and improved function in all groups of patients; see text.	Study not controlled
Orozco et al (2013)	MSC	Knee osteoarthritis	Prospective, observational	Bone marrow aspirate	12	3 months through 1 year	Mean pain score during daily activities decreased from 46.9/100 to 15.4/100 at 12 months. Mean WOMAC pain and function index decreased from 19.4 to 8.3/100.	Small number of patients, study not controlled
Orozco et al (2014)	MSC	Knee osteoarthritis	Prospective, observational	Bone marrow aspirate	11	2 years	The decrease in pain scores remained stable between 12 to 24 months. There was a continual improvement in knee cartilage as measured through MRI.	Extension of above study with the 2 year follow up. One patient did not have significant improvement in first year was excluded in study.
Jo et al (2014)	MSC	Knee osteoarthritis	Prospective, observational	Adipose tissue	18	6 months	In patients receiving high dose of cells, there was a 39% improvement in WOMAC index, along with a 45% decrease in visual analog pain scores.	Study not controlled.

Table 1 (cont.). *Clinical studies in patients with chronic pain.*

Study ID	Stem Cell Type	Disease	Study Design	Source	Number of Patients	Follow up period	Outcome	Comments
Saw et al (2013)	PBSC	Knee osteoarthritis	Randomized, controlled trial	Peripheral blood	50	2 years	Improved IKDC pain/function index from 46.6 to 71.08/100 and 48.68 to 74.82/100 in the control and intervention groups, respectively.	1 patient with DVT in control group and 1 patient lost to follow up.
Wong et al (2013)	MSC	Knee osteoarthritis	Randomized, controlled trial	Bone marrow aspirate	56	2 years	Improvements in multiple indices, see text.	Postoperative procedure.
Vangsness et al (2014)	MSC	Knee osteoarthritis	Randomized, controlled trial	Allogeneic cells from bone marrow aspirate	55	6 weeks through 2 years	Pain scores decreased by a mean of 27.3/100 for low dose patients and 24.1/100 for high dose patients.	Postoperative procedure
Vega et al (2015)	MSC	Knee osteoarthritis	Randomized, controlled trial	Allogeneic cells from bone marrow aspirate	30	1 year	Improvements in multiple indices measuring pain, disability and quality of life. Improvements in cartilage quality.	Non-autologous donor cells used in study.

Abbreviations: WOMAC (Western Ontario and McMaster Universities Arthritis Index), IDKC (International Knee Documentation Committee)

ment or placebo. Furthermore, the majority involve a small number of patients. Larger cohorts of patients need to undergo treatment to more accurately verify whether mesenchymal or hematopoetic stem cells produce an analgesic or restorative effect. Finally, there is variability in terms of whether cell-based therapy is initiated as an isolated minimally invasive procedure or as an adjuvant after surgical measures such as discectomy or fusion; thus, it remains to be seen whether these procedures are cost effective when compared to traditional therapeutic approaches.

Neuropathic Pain

Unlike discogenic pain, neuropathic pain expresses itself in many clinical forms including trigeminal neuralgia and diabetic neuropathy. Studies have attempted to model the clinical effects of cellular intervention. For example, in a recent study, Yousefifard et al (24) described a compression model whereby spinal cord injury (SCI) was induced in rat models with subsequent transplantation of one million BM-MSCs or umbilical cord mesenchymal stem cells (UC-MSCs) into the spinal cord. Both BM-MSC and UC-MSC transplantations alleviated the symptoms of neuropathic pain. The 2 cell groups showed no difference in terms of overall motor recovery and alleviation of allodynia and hyperalgesia. The cells survived in the tissue for at least 8 weeks and prevented cavity formation due to SCI. BM-MSCs have immunomodulatory properties and when administered, may help to minimize neural inflammation and immune mediated injuries. It is theorized that early transplantation of MSCs may improve functional recovery through multiple mechanisms, including the modulation of inflammatory cytokine production, diminished gliosis, promotion of revascularization of the spinal cord via angiogenic effects, and stimulation of the production of bioactive molecules and growth factors. Recently, adipose-derived MSCs have been used to treat neuropathic facial pain in 8 patients who failed pharmacotherapy. Stem cells were injected perineurally into the affected part of the trigeminal nerve; the mean pain score decreased from 7.5 to 4.3 out of 10 points in this group at 6 months (25). In total, 7 out of 9 patients responded positively to their therapy, and 5 of these responders reduced their gabapentin requirement. No serious complications such as infection were reported. In another study, Venturi and colleagues (26) delivered autologous adipose tissue with stem cells trans-perianally to treat pudendal neuralgia that was resistant to medical management. Ten out of 15 patients reported

a substantial decrease in pain scores (from mean of 8.1 to 3.2) at 12 months of treatment as well as an improvement in overall function. No adverse events were reported. Despite the promising results of these studies, both are small and neither were randomized or controlled. While the former study carefully attempted to isolate MSCs, the latter involved direct injection of lipoaspirate containing heterogeneous cells. This makes a link between specific cells and an analgesic response very difficult. However, due to the challenges of treating neuropathic pain and the current limitations of pharmacotherapy, neuromodulation, and integrative therapies, cellular therapy remains a tentative possibility for patients poorly responsive to traditional medication or interventions.

Osteoarthritis

Intraarticular cell therapy has also been used to treat patients with osteoarthritis (OA) or degenerative disease of the joints in the knees and hips for example; this condition can lead to a need for joint replacement, which in turn can result in complications and increased morbidity (27). Degenerative joint disease has been the most thoroughly investigated chronic pain condition treated with cell therapy. MSCs, harvested from bone or fatty tissue, have been the primary cell type used to regenerate and repair joint tissue in patients (28).

MSCs have the ability to differentiate into chondrocytes and repair damaged cartilage tissues. The mechanisms of MSCs for the treatment of osteoarthritis are likely related to the direct differentiation of stem cells into chondrocytes and also paracrine effects via production of bioactive agents. OA models demonstrate that MSCs are able to effectively target and engraft to desired locations. Based on the local environment, these MSCs differentiate into chondrocytes and begin to produce a cartilagenous matrix to repair damaged articular cartilage. Further, therapeutic MSCs modulate local inflammatory conditions and support a more favorable regenerative environment by both a direct secretion of bioactive materials as well as effects on local endogenous cytokine production (29).

The majority of the studies reporting bone marrow MSC transplantation have been observational and have involved small cohorts of patients. One method of cell-based therapy has involved intraoperative incorporation of cells in a gel-matrix. For example, Wakitani et al (30) described a cohort of 24 patients suffering from medial compartment knee OA who received high tibial osteotomy followed by transplantation of bone marrow MSC-embedded collagen gel or gel without cells. Outcomes were measured with a composite score incorporating pain, function, range of motion, muscle strength, flexion deformity, and instability. Both groups endorsed improvements overall at 14.3 and 17.5 months for cell transplant and control, respectively. Although pain scores, overall function, and muscle strength were improved in both groups, there were no statistically significant differences in clinical evaluations between the control and stem cell treated patients. Interestingly, the authors performed "first" and "second" look surgeries when hardware was removed, discovering that cell transplant patients showed improved histology in terms of metachromasia and hyaline-cartilage regeneration.

Other investigators have used direct injection into the knee joint. For instance, an early report by Centeno et al (31) described a patient who received percutaneous intraarticular injection of autologous BMSCs; this individual demonstrated cartilage growth, increased range of motion, and significant decrease in pain score from 4/10 to 0.38/10. The authors then reported a safety study (32) involving 339 patients with various orthopedic diagnoses which showed greater than 85% pain relief in 41.4% of patients, and greater than 50% pain relief in over 60% of a subset of these patients who specifically suffered from knee OA. Davatchi et al (33) reported a small case series of 4 patients who received intraarticular injections of autologous bone-marrow derived MSCs, and followed them monthly for up to a year. Pain scores improved from 80 – 90/100 to 40 – 65/100 at 6 months. Emadedin et al (34) performed fluoroscopically guided injections of autologously collected bone marrow MSC into the knees of 6 patients with OA. At 6 months, the mean pain score decreased from 57/100 to 1/100, although it was reported to increase to 11.6/100 at one year. Evaluation parameters such as walking distance and knee flexion were further found to improve post-procedurally, and no complications were reported. Subsequently, these authors studied another cohort of patients with knee, hip, and ankle arthritis who received injections of MSCs into affected joints (35). All patients who received treatments experienced a decrease in mean pain score from 47 to 17/100 at 6 months, but their pain scores returned to baseline by 30 months, therefore suggesting a time limit to the benefit. Similarly, their WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index, an index used to measure pain, stiffness, and physical function, initially decreased to a nadir at 12 months before increasing again at 30 months.

Other studies have examined clinical improvements together with histological regeneration. For example, Orozco and colleagues (36) have performed investigations which have supported the therapeutic benefit and safety of intraarticularly injected MSCs in knee joints of patients who were not responsive to conservative management. The group initially described a cohort of 12 patients who had failed medical and physical therapy (36). At 12 months, mean pain scores during daily activities decreased from 46.9 to 15.4 with a simultaneous decrement in the WOMAC index scores over the same time period. Magnetic resonance imaging (MRI) T2 quantitative mapping revealed improvements in knee cartilage quality, and no adverse events were reported. The same investigators reported that these patients experienced stable clinical improvement, sustained improvement in pain scores, functionality, and cartilage restoration after 2 years without complications (37). In a dose-response trial, Jo et al (29) reported clinical improvements in pain score and evidence of tissue regeneration after MSC injection in a group of patients with OA of the knee. Specifically, they divided a group of 18 patients into 2 cohorts; the first 9 patients received either a low-, mid-, or high-dose of MSCs in saline, while the next 9 patients all received high doses of cells. Clinically, patients who received a high dose of cells reported the greatest improvement in their pain scores (45%) and WOMAC index (39%) at 6 months, whereas low- and mid-dose patients did not show statistically significant improvement. Interestingly, patients in the low- and high-dose groups also endorsed the greatest improvement in Knee Society Score, an index measuring pain, stability, and range of motion. Finally, cartilage defect size was found to decrease while overall articular cartilage volume was found to increase with cell injection most significantly in the high-dose group. Knee pain was the most common adverse effect and was managed with knee stretching and quadriceps settling exercises. The pain eventually resolved.

Several recent randomized clinical trials have reinforced the benefits of MSC injection for patients with joint disease. Saw et al (38) divided 50 patients into 2 groups, randomizing them to a series of intraarticular injections of hyaluronic acid or peripheral blood stem cells after knee arthroscopy and chondroplasty. These administrations occurred up to 6 months after surgery. Patients in both groups endorsed similar improvements in their knee function as reflected by the International Knee Documentation Committee (IKDC) index score (a measurement tool reflecting pain and activity level) at 24 months, although patients who received peripheral blood stem cells showed increased quality of cartilage on second-look arthroscopy and core biopsy. Similarly, Wong et al (39) compared 56 patients who received either injections of autologous MSC with hyaluronic acid or hyaluronic acid alone after undergoing knee arthroscopy and medial opening high tibial osteotomy with locking plate surgery. They found that while both treatment groups had improvements in pain, activity, and function, as measured through multiple indices (including the IKDC, Lysholm, and Tegner scales), the cell therapy group exhibited an added benefit of 7.65/100 on IKDC, 7.61/100 on Lysholm, and 0.64/10 for Tegner (all statistically significant). MRI also revealed more favorable improvements in cartilage regeneration with cell therapy. In another study, Vangsness et al (40) investigated 55 patients receiving partial meniscectomies who were randomized to postoperative injections of either sodium hyaluronate or one of 2 different doses of allogeneic MSCs (50×10^6 or 150×10^6), and followed these patients over 2 years. Patients who received the low dose of MSCs had a baseline pain score of 56/100 and reported an improvement of 27.3/100 at 2 years; similarly, high-dose patients had a baseline pain score of 43.1/100 and reported an improvement of 24.1/100 at 2 years. In comparison, a minimal overall change in pain score was observed by the control group. Vega and colleagues (41) performed a randomized controlled trial of 30 patients with chronic knee OA; they compared injections of allogeneic bone marrow stem cells with hyaluronic acid injections and found that cell-therapy patients described approximately a 40% decrease in pain compared to 20% in controls. Disability and quality-of-life indices were similarly impacted. This study also highlighted that allogeneic cells could be used safely and effectively. In terms of safety, Peeters et al (42) performed a meta-analysis of 844 procedures and joint injections, and evaluated 8 distinct studies involving autologous MSCs. They found 4 incidents of serious adverse events (one bone marrow aspiration-related infection, one pulmonary embolism, 2 tumors not at site of injection), 22 cases of procedural complications, and 7 cases of stem cell-product related adverse events (42). The low number of adverse effects supports the relative safety of these procedures.

In a closer examination of the mechanisms underlying cartilage restoration, Kuroda et al (43) used a rabbit anterior cruciate ligament transection (ACLT) model to demonstrate that intraarticularly injected adipose-derived stem cells (ADSCs) inhibited the progression of

cartilage degeneration by secreting a liquid factor that produced chondro-protective effects such as chondrocyte proliferation and cartilage matrix protection. OA progression was milder in the ADSC treated knees than in the control knees 8 weeks after ACLT in both macroscopic and histologic evaluation. The mechanism by which ADSC therapy facilitates tissue repair is unclear, but current theories suggest that ADSCs directly fill the lesion to regenerate tissue, and that ADSCs stimulate the secretion of bioactive factors such as cytokines and growth factors. Data from the study showed that the paracrine effects of ADSCs regulate chondrocyte viability in OA. Injected ADSCs homed into intraarticular soft tissue and contributed to the inhibition of cartilage degeneration progression. TNF-α activity, which normally leads to chondrocyte death, was also found to be suppressed when chondrocytes were co-cultured with ADSCs. Moreover, the production of MMP-13 in articular chondrocytes, which damages cartilage in OA, was reduced when they were treated with injected ADSCs in vivo and in vitro, suggesting that ADSCs protect articular cartilage from degeneration by inhibiting MMP-13 expression.

Musculoskeletal Diseases

The use of allogeneic and autologous MSC therapies for the treatment of musculoskeletal diseases and dysfunctions has received increasing attention. There are many on-going in-vitro and in-vivo investigations on the effects of transplantation of multipotent mesenchymal stromal cells for regenerating the musculoskeletal system. Here, we will highlight a few of the possible applications for MSC therapy.

Cartilage is avascular and aneural, therefore; articular cartilage usually does not regenerate after injury or damage. Meniscal lesions are one of the most frequently injured. Because of the poor healing capacity of the meniscal lesions in the avascular inner zones, treatment mainly focuses on removing portions of the damaged meniscus, which subsequently predisposes the knee joint to degenerative changes (44). Although meniscus suturing can repair meniscal tears, recent meta-analysis suggests a high failure rate in terms of long-term outcomes (45). Regenerative treatment of the meniscus with MSCs seems to be an exciting approach for healing meniscal tears and defects. However, it is still not clear whether the benefit of stem cell therapy is a direct effect of the mesenchymal-based cells or a response mediated by secretion of certain stimulating factors (44).

Autologous somatic stem cells and BMSCs can also be used for cartilage transplants. For example, Yamasaki et al (46) described patients with injured articular cartilage who were treated with BMSC transplantation and subsequently reported improvement in pain and ambulation 6 months after transplantation. Follow-up arthroscopy 2 years after the first transplantation and one year after the second transplantation revealed that the defects had been repaired and replaced with fibrocartilage. Studies in the past have shown that injecting MSCs at injury sites can increase the speed of Achilles tendon healing in animal models (47,48).

Idiopathic osteonecrosis of the femoral head (ION) is a painful disorder that progresses to collapse of the femoral head and destruction of the hip joint. Aoyama et al (49) performed a prospective study to assess the safety and efficacy of transplantation of cultured autologous BMSCs mixed with b-tricalcium phosphate (b-TCP) in combination with vascularized bone grafts for the treatment of advanced stage ION. Ten patients with stage 3 ION were enrolled. After a 12-week rehabilitation program, all patients reported reduced pain and increased physical function with no serious adverse events reported in the study (50). The study was limited by a small sample size and no control.

It is unclear whether transplanted cells exert therapeutic effects via direct differentiation to osteogenic cells. Earlier studies on cell transplantation were designed and performed with the aim of engrafting transplanted cells to regenerate the tissue. However, recent studies showed that this was not the case. Only a small proportion of MSCs, locally or systemically administrated, will actually be incorporated into injured tissues, which indicates that the beneficial effects of tissue repair and regeneration are more likely indirect and depend on the paracrine activity of MSCs. Müller et al (51) reported promising results in their study with 5 patients with osteonecrosis who were treated with MSCs. Results revealed clinical improvement in pain and tolerability of daily activity, and no significant complications were noted.

In sum, clinical trials of cell-based therapies have yielded intriguing results. OA has been the subject of the majority of clinical studies. Both prospective observational and controlled studies have reported decreased pain and improved function among treated patients. A few of these studies have even described regeneration of cartilage upon follow-up imaging. Unfortunately, the majority of these studies were not blinded or controlled, and many have limited follow-up (up to one

or 2 years). While clinical outcomes are clearly easier to assess, mechanistic and histological details are more complex to examine due to the obvious invasiveness of performing a biopsy and tissue collection; yet, this is important to consider since it is important to ascertain how mesenchymal or hematopoetic stem cells exert their therapeutic effects. Moreover, studies showing efficacy in these small groups may not be reflected in larger cohorts due to placebo effect or other confounding factors.

Risks and Potential Adverse Effects

As discussed throughout this article, there are theoretical and realized risks to cell-based therapies. Clinically, there have not been significant adverse events reported in the majority of trials. Most studies reported minimal to no adverse effects or complications. In a systematic review of the literature, Peeters et al (15) found that in a total of 844 intraarticular procedures, only 4 serious adverse events occurred, including one bone marrow aspiration site infection, one pulmonary embolism, and 2 tumors at a mean of 21 months follow-up. Other adverse events reported in their study were less severe and self-limited, including pain, swelling, urticaria, transient transaminitis, and tingling at site of blood draw. Subsequently published studies have failed to reflect excess adverse side effects. However, it is important to note that processes such as malignancy may require a longer period to develop, and that these untoward consequences may exist outside the range of study follow-up. Jo et al (29) showed a very low incidence of infection (0.002%) in intraarticular injection of autologous adipose tissue derived MSCs in patients with knee osteoarthritis. Emadedin et al (34) also showed no severe adverse effects except for a few patients who experienced very minor localized adverse effects such as rash and erythema. Autologous BMSCs appear safe because their use does not lead to either immunological actions or disease transmission. On the other hand, they may carry the risk of tumor production during a long-term follow-up period. While some studies have shown no evidence of tumor formation after transplantation of BMSCs into immunodeficient animals, a few papers have suggested the potential for cancer progression (52). For instance, one study by Rosland et al (52) reported spontaneous malignant transformations in 45.8% of cases of BMSCs grown in long-term cultures (5 – 106 weeks). These transformed mesenchymal cells were unable to undergo complete differentiation in soft agar assays, showing high tumorigenicity with an increased proliferation rate and altered phenotypic morphology that caused multiple fast-growing lung lesions when injected into immunodeficient mice. Thus, spontaneous malignant transformation may confer a safety risk in long-term ex vivo expansion of MSCs.

Ongoing Clinical Trials Using Cell-based Therapy

There are a number of ongoing clinical trials involving degenerative disease of the spine, joints, and neuropathic pain and mixed conditions that reflect multiple clinical areas of interest. The majority of ongoing studies are early stage, Phase I or II clinical trials that explore safety and efficacy, which should be of interest to current practitioners (Table 2). As previously discussed, results from prior studies have been intriguing and there are opportunities for patients to enroll in current studies. The large number of investigational studies demonstrates the burgeoning interest in biologic therapies as a means of achieving tissue regeneration and complete healing. Thus, we hope that this review provides opportunities for more robust investigations, particularly for patients who have failed conventional management with medications or procedural interventions.

Discussion/Conclusion

This review discusses the utility of stem cells as a novel therapeutic strategy for discogenic pain, neuropathic pain, and OA, all of which are inadequately treated with existing pharmacological or interventional methods. While there are a number of published observational and even controlled clinical investigations reporting improvements in various indices that measure pain and dysfunction, many of these outcomes are preliminary, and lack controls, blinding, or sufficient patients for an adequately powered study. Furthermore, many ongoing studies are still recruiting patients and have yet to yield preliminary data on reported outcomes. While there are few reported serious adverse events (as discussed in a recent meta-analysis), there still exists a possibility for longer term side effects not yet captured in study follow-up. Therefore, patients with chronic pain conditions refractory to conventional therapy who consider cell-based therapies should approach the treatment with caution. Finally, studies of cell-based therapy are not widely available. Patients who are interested in enrolling in trials most likely need access to an academic or tertiary medical center with the capabilities of collecting, culturing, and delivering

Table 2. *Current clinical trials both in the United States and internationally.*

Location	Modality	Cell Type	Indication	Clinical Trial ID	Enrollment	Phase (if applicable)
USA	Allograft			NCT01771471	Active, not recruiting	Phase II, DB
USA	Allograft	MPC	Lumbar back pain	NCT01290367	Ongoing, not recruiting	Phase II, DB
USA	Autologous	Adipose stromal cell	DJD	NCT02097862	Actively recruiting	NR, Open Label
Spain	Allogeneic	BM MSC	DDD	NCT01860417	Ongoing, not recruiting	Phase I, DB
Austria/Germany	Autologous	Chondrocytes (IVD?)	DJD, herniation	NCT01640457	Actively recruiting	I/II Open Label, Randomized
Korea	Autologous	Adipose MSC	DJD	NCT01643681	Active recruitment	Phase I/II Non-Randomized, Open Label
Egypt	Autologous	MSC	Diabetic neuroapthy	NCT02387749	Ongoing, not recruiting	Phase II/III Open Label, Single Group Assignment
USA	Autologous	MSC	DJD	NCT02529566	Enrolling, Invitation only	Observational, Cohort
Korea	Autologous	Peripheral blood SC	Diabetic neuropathy	NCT02315235	Actively recruiting	Single Blind, Randomized
India	Autologous	Bone marrow SC	Osteoarthritis	NCT01152125	Enrollment by invitation	Phase I/II Open Label, Single Group Assignment
Korea	Autologous	Adipose MSC	Rotator Cuff Disease	NCT02474342	Recruiting	Open Label, Single Group
USA	Autologous	BM aspirate	Knee Osteoarthritis	NCT01931007	Ongoing, not recruiting	Phase I Randomized, Single Group
USA	Autologous	Adipose MSC	Osteoarthritis	NCT02241408	Recruiting	Observational, Cohort
USA	Autologous	Fat grafting	Amputation stump pain	NCT01645722	Ongoing, not recruiting	Open Label, Efficacy
Iran	Autologous	BM stem cell	Knee OA	NCT00550524	Enrolling by invitation	Phase I, Open Label, NR
USA	Autologous	Adipose-derived MSC	Knee OA	NCT01739504	Recruiting	Phase I/II, Open Label, Single Group Assignment
Vietnam	Autologous	Tissue scromal vascular fraction	Knee OA	NCT02142842	Ongoing, not recruiting	Phase I/II, Single Blind, Single Group
Spain	Autologous	MSC	Knee OA	NCT02123368	Ongoing, not recruiting	Phase I/II, Open Lavel, Randomized
China	Autologous	Adipose MPC	Knee OA	NCT02162693	Ongoing, not recruiting	Phase II, Randomized, Single Blind
Canada	Autologous	MSC	Knee OA	NCT02351011	Currently recruiting	Phase I/II Open Label, Non-Randomized

cells. Nevertheless, more and more private clinics are offering stem cells as treatment, therefore access is ever expanding outside the scope of clinical investigations in academic centers. We believe there is exciting potential for stem cell therapy to benefit chronic pain conditions with more rigorous study.

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