Retrospective Study

Pain Relief After Allogenic Stem Cell Disc Therapy

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Background: Treatment of intermediate-stage painful degenerative disc disease is controversial, with few reliable options. Allogenic mesenchymal stem cells (MSCs)are an alternative to autologous stem cell transplantation. Allogeneic MSCs in the treatment of discogenic low back pain have some practical advantages, ranging from availability to ease of treatment in a procedure-room setting.

Objectives: To assess the efficacy and safety of allogenic MSC injection into painful lumbar intervertebral discs and associated clinical outcomes.

Study Design: Retrospective observational cohort study.

Setting: Private practice.

Methods: There were 33 patients: 15 women and 18 men with an average age of 47.6 years. The patients' average follow-up was 26.88 months Patients were treated with intradiscal injection of approximately 5 million allogeneic polyclonal MSCs in 1% hyaluronic acid derived from immunoselected umbilical cord stem cells. Patients were monitored for adverse event reactions. Clinical outcomes were assessed with reductions in the reported Visual Analog Scale (VAS) for back pain, the Oswestry Disability Index (ODI) scores, and the use of the modified Macnab criteria.

Results: No patient required any additional treatments for low back pain stemming from the level treated with MSC injections. At a 2-year follow-up, the average VAS low back score reduction was 6.565 ± 1.619 and 38.333 ± 14.865 for the ODI ($P < 0.001$). Reported Macnab outcomes were excellent in 11 patients (33.3%), good in 19 (57.6%), and fair in 3 (9.1%).

Limitations: Our observational study is limited by patient selection, hindsight bias, and low patient numbers.

Conclusion: The results of our feasibility study suggest that the injection of allogeneic MSCs to treat patients with painful intermediate-stage degenerative disc disease has merit. No adverse reactions were observed. The authors recommend further study in a randomized prospective study setting with a placebo control group or a natural history study group of patients to solidify this research.

Key words: Allogeneic, mesenchymal stem cells, low back pain, degenerative intervertebral disc disease

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Since 2000, the biotech industry has generated many developments and new treatments that have improved health care and benefited patients. Many areas of clinical medicine are being transformed through advances in regenerative medicine, a field that includes cell therapy, gene therapy, and tissue engineering (1-4). Significant advancements in regenerative medicine employ biological treatments such as platelet-enriched plasma (5-8), stem cells (3,9), and the by-products obtained from their culture. Regenerative medicine treatment approaches have been reported to provide long-lasting relief and, in some cases, even curative results (10-12). A recent systematic review and single-arm meta-analysis by Sanapati et al (13) found variable degrees of evidence supportive of mesenchymal stem cells (MSCs) and platelet-rich plasma being effective in managing discogenic low back pain, radicular pain, facet joint pain, and sacroiliac joint pain.

Allogeneic stem cell transplantation has been gaining more attention in the last decade as an alternative to autologous bone marrow concentrate transplants (14-17). One of its main advantages is the reduction of functional variability by combining cell products from multiple donors in a master bank. MSCs can be transplanted as allogeneic cells with a low risk of rejection (18). The authors studied the safety of MSC treatment and whether it can improve chronic low back pain (CLBP) symptoms and patient functioning while forming the basis for future studies into the efficacy and safety of these allogeneic stem cell-based treatments. The primary endpoint of our clinical investigation was to determine the safety of a single injection of allogeneic MSCs in an office setting into a symptomatic lumbar disc and to analyze clinical improvements in patients with CLBP associated with moderate DDD.

Methods

Patients

Patients were recruited from 4 participating study sites from December 2017 through November 2018. Patients were followed for a minimum of 24 months. The average follow-up was 26.88 months. There were 33 patients consisting of 14 women and 18 men with an average age of 47.6 years. Since MSCs are currently considered a biological product, not a drug, and are widely used in the treatment of graft versus host disease (GvHD) (19), degenerative osteoarthritis (20-22), and many other pathologies, this case study did not require US Food and Drug Administration approval and was not registered with clinicaltrials.gov. The study's institutional review board approval number is CEIFUS 106-19.

Inclusion/Exclusion Criteria

Inclusion criteria were 1) documented diagnosis of moderate DDD (see below) at one level from L1 to S1, 2) chronic low back pain for at least for 12 months with a VAS back pain score of 5 or higher, 3) 3 months of failed conservative treatment, and 4) a Pfirrmann grade of III to V. Patients were excluded from the study if they had 1) comorbid conditions affecting disc health such as metabolic diseases, 2) infection, 3) trauma, 4) spondylolisthesis, 5) radiculopathy, 6) claudication symptoms from foraminal, lateral or central canal stenosis, or 7) tumors. These inclusion and exclusion criteria resulted in a study population of 33 patients. Statistical power analysis predicted that this study size was sufficient to assess the safety of injecting allogenic MSCs into painful degenerative intervertebral discs in this observational cohort study.

Diagnostic Algorithm

Initially, provocative lumbar discography was performed to determine if the target disc identified by history taking, clinical examination, and magnetic resonance imaging MRI review was the pain generator. The MRI grading by Pfirrmann (23) was purposefully not employed to stratify patients with CLBP for allogeneic MSC treatment as it correlates poorly with clinical symptomatology. However, it was used to grade patients before and after the allogenic MSC injection to assess any visualized structural changes suggestive of healing seen on the posttreatment MRI scan..

Stem Cell Harvest & Expansion

Allogenic MSCs were derived from the mononuclear cell fraction of the umbilical cord. With the mother's informed consent, umbilical cord MSC samples were obtained immediately after delivery (24,25). After procurement, cells were expanded ex-vivo by clear preservation and storage procedures at a contract manufacturing facility operating under current good manufacturing practice conditions. These mesenchymal stem cells were derived from Wharton's jelly and share an identical genetic makeup and physiology of the newborns (26). For this purpose, samples of the umbilical cord approximately 10 cm in length were collected aseptically and immediately placed in a collection cup containing a culture medium and an antibiotic solu-

tion. Samples were stored at 4°C while en route to the lab. the Wharton's jelly was excised to about 1 – 2 mm pieces and then transferred to 100 mm dishes coated with 0.2% gelatin.

Two grams of Wharton's jelly tissue were plated per dish and covered entirely with the culture medium consisting of low-glucose Dulbecco's Modified Eagle's Medium supplemented with fetal bovine serum, penicillin, and streptomycin. Half of the culture medium was changed on day 5 without disturbing the tissue pieces. On day 8, all the tissue pieces were removed, and the culture medium was completely replaced with fresh medium. Wharton's jelly MSCs were maintained in cultures at 37°C in a humidified atmosphere containing 5% CO_2. The medium was changed until 80% confluence was reached. For cell passage, 0.05% trypsin- ethylenediaminetetraacetic acid (EDTA) was used to dissociate the cells and neutralize them from the culture medium. The cells were then washed once with phosphate-buffered saline and collected by centrifugation. The cells were seeded at 1 × 104 cells/cm^2.

After isolation, the cells were expanded only to passage 5 for clinical application, where they were assumed to be pluripotent. MSC expansion was limited to 5 passages to avoid cell differentiation and function decline. Cell procurement, processing, cryopreservation, and storage procedures were performed at a contract manufacturing facility (Vidacel) accredited by the Association for the Advancement of Blood & Biotherapies under current good manufacturing practice conditions. The cell count characterized the product's viability by trypan blue exclusion, and human leukocyte antigen class II (HLA-DR). The expressions of mesenchymal cell surface markers CD44, CD90, CD105, and CD34 were assessed by flow cytometry. The product was examined for donor infectious diseases (hepatitis B virus, hepatitis C virus, human immunodeficiency viruses 1 and 2, human T cell lymphotropic virus types 1 and 2, trypanosoma cruzi, treponema pallidum), sterility (aerobic and anaerobic bacteria, fungi), endotoxins, and mycoplasma. The cells were placed in sterile containers and cryopreserved. The cryopreserved products were shipped to the clinical sites "ready for use" where the clinical practitioners injected the cells into the target disc.

Intervertebral Disc Injection Procedure

We used a standard posterior lateral approach under fluoroscopic guidance with an 18G needle for the injection, employing a similar protocol utilized during provocative discography. Patients were positioned prone and sedated with monitored anesthesia care protocols.

Before and after the injection, they received an oral antibiotic prophylactic of second generation cephalosporin or quinolone if drug allergies prevented second-generation cephalosporins by mouth. Patients were injected with approximately 5 million allogenic progenitor cells in 1% hyaluronic acid, which is a commonly employed, commercially available injection vehicle for human MSCs (27,28).

After the injection, they were monitored for another 30 minutes in the recovery area, where vital signs were monitored until discharge to exclude any anaphylactic reaction. The discharge criteria were stable vital signs in an otherwise comfortable patient. A schematic of the presumed biological action (Fig. 1) and the MSCs injected into the painful intervertebral disc are shown in Fig. 2.

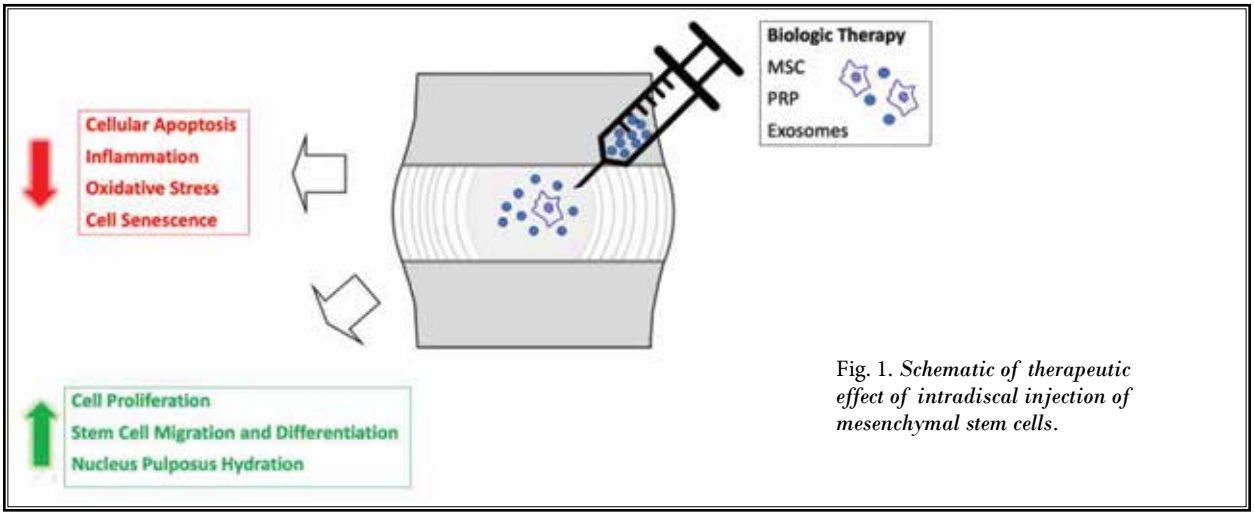

Fig. 1. *Schematic of therapeutic effect of intradiscal injection of mesenchymal stem cells.*

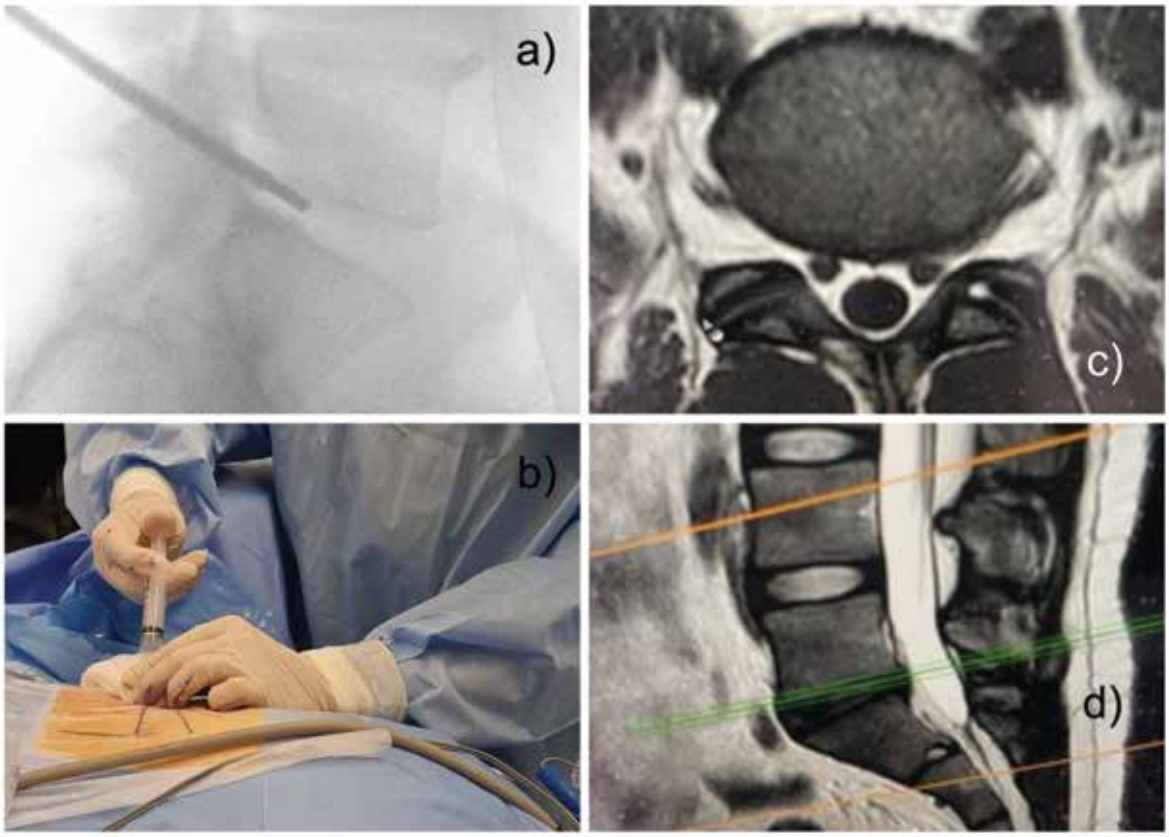

Fig. 2. *An exemplary patient being treated with intradiscal injection of 5 million allogeneic progenitor cells in 1% hyaluronic acid for painful intermediated degenerative disc disease at L5/S1 validated by provocative discography.*

Outcome Assessment & Statistical Analysis

Primary clinical outcome measures assessing the effectiveness of allogeneic MSCs in reducing CLBP were the modified Mcnab criteria (29), VAS low back pain (30), and the Oswestry Disability Index (ODI) (31). Patients were clinically and radiographically evaluated at 3, 6, 12, and 24 months posttreatment. Additionally, patients were interviewed about any adverse events. These patient-reported outcome measures were correlated with clinical improvements in the postinjection MRI-Pfirrmann scoring (23) of the healing lumbar intervertebral disc whenever postoperative scans were available.

The treatment's ultimate success was determined if no postinjection interventions directed at the treated disc level were necessary at the final follow-up. Descriptive statistics tests were performed on demographic and outcome data using IBM SPSS Statistics 27 (IBM Corporation). Products were tested for statistically significant improvements by employing a paired t test. The analysis did not include missing numbers.

Results

In our feasibility study, there was no adverse treatment effect except for one patient who experienced severe low back pain for one day. No patient required any additional treatments for low back pain stemming from the level treated with MSC injections. Twenty-two of the 32 patients had a 2-year follow-up. The available study patients' mean VAS score for low back pain improved at each of the scheduled and final follow-up visits from preoperatively 8.22 ± 1.43 (n = 32), to 3.31 ± 1.78 at one month (n = 32), 2.57 ± 1.67 at 3 months (n = 28), 2.03 ± 1.38 at 6 months (n = 30), 1.81 ± 1.50 at one year (n = 27), and 1.74 ± 1.32 at 2 years postoperatively (n = 23; Table 1). It was statistically significant ($P < 0.001$) at one month postoperatively and at each follow-up visit after that (Table 1). The overall VAS score reduction at the 2-year follow-up was 6.565 ± 1.619 ($P < 0.001$).

The ODI score also improved at a statistically sig-

nificant level ($P < 0.001$). The available study patients' mean ODI score improved at each of the scheduled and final follow-up visits from preoperatively 44.81 ± 14.35 (n = 32), to 19.58 ± 11.62 at one month (n = 32), 15.38 ± 12.83 at 3 months (n = 29), 13.48 ± 10.16 at 6 months (n = 31), 11.80 ± 10.61 at one year (n = 30), and 6.07 ± 8.34 at 2 years postoperatively (n = 30; Table 2). At the 2-year follow-up, the ODI reduction was 38.333 ± 14.865 ($P < 0.001$; Table 2). The average preoperative Pfirrmann grading was 4.05 ± 0.72. It improved to 3.65

Table 1. *Means and paired sampled t test results of pre- and postoperative VAS scores for low back pain after allogeneic cell injections at scheduled follow up and final visit.*

VAS Back	Mean	n	Std. Deviation	Std. Error Mean
Preop VAS	8.22	32	1.431	.253
Postop VAS one month	3.31	32	1.786	.316
Postop VAS 3 months	2.57	28	1.665	.315
Postop VAS 6 months	2.03	30	1.377	.251
Postop VAS one year	1.81	27	1.495	.288
Postop VAS 2 years	1.74	23	1.322	.276

VAS Reduction	Mean	Std. Deviation	Std. Error Mean	95%CI of the Difference		t	df	Significance	
				Lower	Upper			One-Sided P	Two-Sided P
Preop VAS - Postop VAS one month	4.906	1.990	.352	4.189	5.624	13.949	31	< .001	< .001
Preop VAS - postop VAS 3 months	5.500	2.134	.403	4.672	6.328	13.635	27	< .001	< .001
Preop VAS - postop VAS 6 months	6.167	2.001	.365	5.419	6.914	16.876	29	< .001	< .001
Preop VAS - postop VAS one Year	6.370	1.644	.316	5.720	7.021	20.131	26	< .001	< .001
Preop VAS - postop VAS 2 years	6.565	1.619	.338	5.865	7.265	19.450	22	< .001	< .001

VAS= visual analog scale

Table 2. *Paired sampled t test of pre- and postoperative ODI scores reductions for low back pain after allogeneic cell injections and at scheduled follow-up and final visit.*

	Mean	n	Std. Deviation	Std. Error Mean
Preop ODI	44.8125	32	14.34919	2.53660
Postop ODI one month	19.6875	32	11.61878	2.05393
Postop ODI 3 months	15.38	29	12.830	2.382
Postop ODI 6 months	13.48	31	10.158	1.824
Postop ODI one year	11.80	30	10.601	1.935
Postop ODI 2 years	6.07	30	8.346	1.524

ODI Reduction	Mean	Std. Deviation	Std. Error Mean	95%CI of the Difference		t	df	Significance	
				Lower	Upper			One-Sided P	Two-Sided P
Preop ODI – Postop ODI one month	25.125	14.430	2.550	19.922	30.327	9.849	31	< .001	< .001
Preop ODI - Postop ODI 3 months	30.137	16.448	3.054	23.881	36.394	9.867	28	< .001	< .001
Preop ODI - Postop ODI 6 months	31.161	16.802	3.017	24.997	37.324	10.325	30	< .001	< .001
Preop ODI - Postop ODI one Year	33.800	15.855	2.894	27.879	39.720	11.676	29	< .001	< .001
Preop ODI - Postop ODI 2 years	38.333	14.865	2.714	32.782	43.884	14.124	29	< .001	< .001

ODI=Oswestry Disability Index

± 0.81 at the final follow-up 2 years postoperatively. The Pfirrmann grade improvements were statistically significant on two-sided paired t testing with a *P* value of < 0.001. Representative pre- and post-treatment MRI scans are shown in Fig. 3.

Patients improved significantly within one month from the in-office intradiscal MSCs injection, with 74.73% of the VAS reduction for low back pain and 65.54% of the ODI reduction materializing in the immediate postoperative period. Postprocedural Macnab outcomes were also favorable in the majority of patients reporting: excellent (11; 33.3%), and good (19; 57.6%) outcomes. Only 3 patients (9.1) reported fair Macnab outcomes at final follow-up (Table 3).

Discussion

In most cases CLBP is caused by degeneration of the intervertebral disc. This type of pain, in severe cases, can radiate to the lower extremities. It can affect quality of life and is one of the leading causes of missed work days.

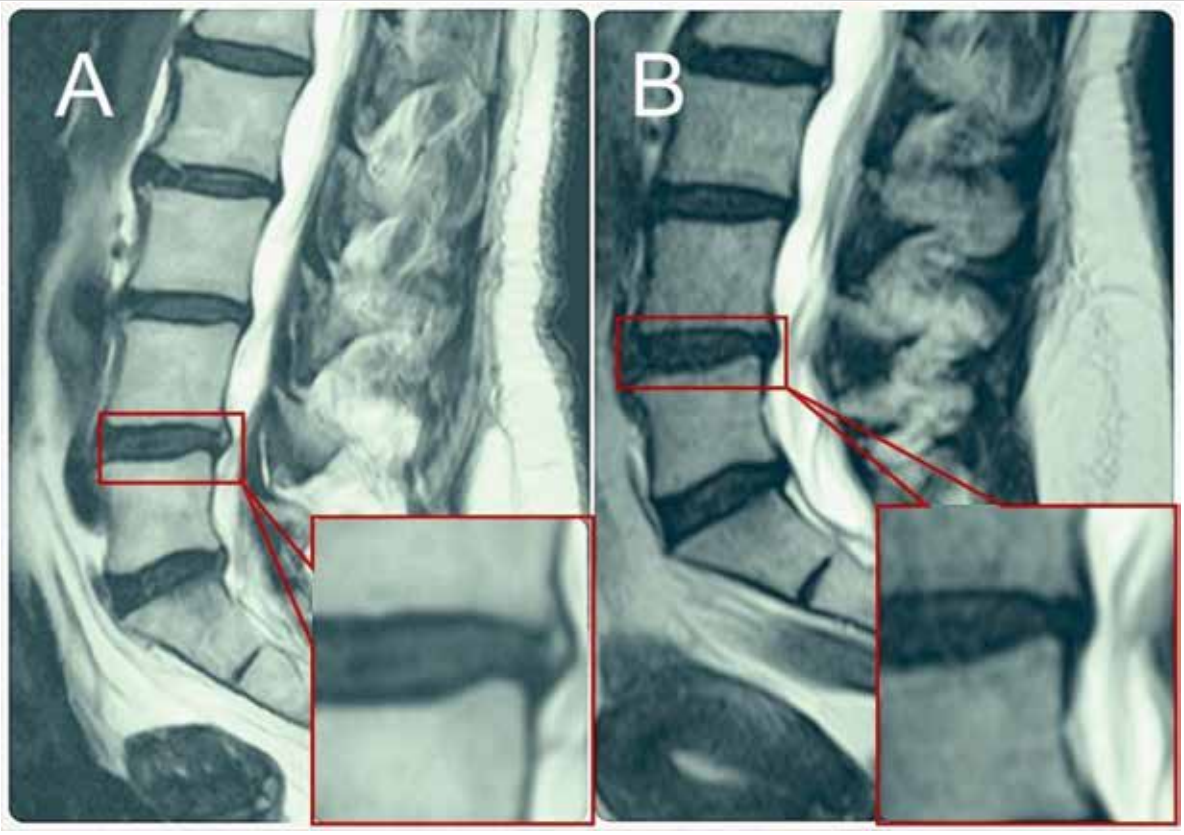

Fig. 3. *An exemplary patient treated with intradiscal injection of 5 million allogeneic progenitor cells in 1% hyaluronic acid for painful intermediated degenerative disc disease at L4/5. The preoperative sagittal T2-weighted MRI scan (A) showed Pfirrmann grade III disc degeneration with an annular tear (cutout A). The one-year follow-up MRI scan (B) suggests that the intradiscal allogeneic progenitor cells injection seems to have promoted healing of the annular tear (cutout B).*

Table 3. *Postoperative Macnab outcomes at final follow-up.*

	Frequency	Percent	Valid Percent	Cumulative Percent
Excellent	11	33.3	33.3	33.3
Good	19	57.6	57.6	90.9
Fair	3	9.1	9.1	100.0
Total	33	100.0	100.0	

The medical burden from CLBP is substantial; degenerative lumbar disc disease has become a global social and economic problem (32,33). The condition is ubiquitous among middle-aged and older adults throughout the world. Existing treatment options include approaches such as anti-inflammatory drugs, physical therapy, interventional treatments, medical therapies, and spinal surgery. The primary surgical interventions are discectomy, disc replacement, and interbody fusion. The latter, however, is prone to cause deterioration of adjacent segments due to the destabilizing effect of the surgical exposure and the increased stress imparted onto the spine by the metal implants. Motion preserving nonfusion surgery with artificial disc replacement has problems, such as failure of the device and heterotopic ossifications around the implant (34-38).

There are dozens of companies and programs focusing on next-generation approaches applying the same concepts using allogeneic platforms that could be managed "ready to use" and would be more scalable and cost-effective (6). According to the Alliance for Regenerative Medicine (39), more than 1,000 companies worldwide are developing regenerative medicine treatments and technologies.

A search of ClinicalTrials.gov reveals that MSCs are being tested in roughly 1,300 clinical trials for cell therapy, gene therapy, tissue-engineered, and combination products. In addition, almost 600 of them are in Phase II, and about 100 are already in Phase III. Several of these studies focus on diseases that have a significant effect on an aging society. Health problems associated with age are an area with a substantial effect of regenerative medicine that grows yearly. MSCs are being studied in clinical trials for indications that include orthopedic injuries, GvHD following bone marrow transplantation, cardiovascular diseases, autoimmune diseases, and liver diseases (40-43).

Preclinical and clinical studies increase annually, showing a sustainable and growing development that has already begun to show results with several authorized products globally. Further research may be required to harness its full therapeutic potential. Still, it is predictable that substantial advances will be made in the utility of biological therapies for the regenerative and immunomodulatory treatment of various pathologies. To date, clinical studies have indicated that stem cell administration is a promising and safe therapeutic approach (9,24,25,44-48). Depending on the tissue donor, stem cell therapy can be classified into autologous and allogeneic. Autologous stem cells are used as they are readily available from many tissue sources, have a lower risk of complications, and are free from ethical concerns. To date, autologous stem cell transplantation has been performed for many purposes (14,45,49) including promoting cardiac (50) and cartilage regeneration, accelerating wound healing, and improving cosmetic appearance.

Several studies and works on platelet-rich plasma, stem cells, and biological therapies in disc degeneration and low back pain have been published showing that these treatments have great potential to become routine procedures, given their safety and efficacy (51-56).

MSC product approvals are at a relatively early stage. The Ministry of Food and Drug Safety (the Republic of Korea's counterpart to the US Food and Drug Administration) approved CARTISTEM, an MSC product derived from umbilical cord blood developed by MEDIPOST Co., Ltd to treat degenerative or traumatic osteoarthritis (57). Cupistem (Anterogen Co., Ltd) is an autologous adipose tissue-derived MSC product to treat anal fistulas in patients with Crohn disease. Regulatory agencies in Canada and New Zealand approved Prochymal (Osiris Therapeutics), which contains allogeneic bone marrow-derived MSCs to treat steroid-resistant GvHD in children. The European Medicines Agency approved darvadstrocel (Alofisel) from Takeda Pharma and TiGenix, the first MSC-derived advanced therapy medicinal product in Europe, to treat complex anal fistulas in adults with Crohn disease. TEMCELL, developed by JCR Pharmaceuticals based on Osiris technology, is approved for marketing and reimbursement in Japan for the treatment of GvHD. HeartSheet (Terumo, approved in Japan) and Cellgram-AMI (Pharmicell Co., Ltd) approved in the Republic of Korea) are other products made containing MSCs. In the United States, Mesoblast, Inc. proposed remestemcel-L (Ryoncil) for treating GvHD treatment in children under 12 years of age, but the FDA in its latest ruling did not approve the drug for that use (57).

More recently, the research focus has shifted from MSCs to components derived from MSCs. These components include MSC extracts, microvesicles, and exosomes to perform specific biological activities. Like MSC cells, MSC exosomes have shown an ability to repair tissue damage, suppress the inflammatory response, and modulate the human immune system (50,58-61).

MSC treatment of painful degenerative disc disease has not been widely attempted; our current study was merely focused on establishing its feasibility. It does not constitute a formal clinical trial with control

groups, which is one of our study's main limitations. Other limitations include the selection of patients with a single-level disease. This patient selection criterion was chosen to minimize the effect of any other confounding factors and simplify the analysis. However, in real-life scenarios, patients with multilevel painful degenerative disc disease are likely more common, and our therapeutic approach of injecting allogenic MSCs into painful degenerative lumbar discs should be formally studied in these patients.

Our feasibility study showed safe and efficacious treatment for chronic low back pain in patients with moderate lumbar DDD. No infection, allergic reaction, or symptoms consistent with a GvHD immune response was observed. The injection of MSCs into a painful diseased disc is an addition to the portfolio of minimally invasive treatments and an alternative to medical pain management and spinal surgery. Over 2 years, our study patients demonstrated durable clinical symptom relief and MRI improvements over the 2-year follow-up period with the average Pfirrmann grading improved to a statistically significant level ($P < 0.001$) from 4.05 ± 0.72 to 3.65 ± 0.81. In comparison, it is well known that virtually all types of conservative therapies for low back pain may have efficacy but limited duration, thus, adding to the public health crisis due to the potential for substance dependence or worse, increased morbidity due to opioid abuse.

Our study results are promising as they demonstrate significant improvement in pain and function throughout the postintervention follow-up period. However, they are limited by the study's observational nature in a small group of patients and only provide low-grade clinical evidence that is subject to selection and hindsight bias.

In addition, current radiographic methods may not be sensitive enough to detect changes that may significantly affect pain and function in the postprocedure follow-up. In the future, when higher-field MRI scans are more widely available, intervertebral disc structural changes at a more granular level may be detectable. We did not overemphasize the postintervention MRI analysis of this study since the correlation between clinical symptomatology and MRI appearance on a routine lumbar MRI scan is poor (62-69). The assessment of the intervertebral disc's structural changes may offer insights into optimizing an MSC treatment strategy. It should be analyzed as such whenever technically possible. Even without understanding the mechanisms of action and their MRI equivalents, the changes from baseline analysis in our patients showed a reduction in VAS and ODI scores following MSC treatment.

Conclusions

Allogeneic MSC injection is an alternative to autologous material. Tissue banks make it available, thus simplifying the process of procurement and expansion. Our initial feasibility study results show significant improvement in pain scores and clinical functioning with a reduction in ODI scores. The postinjection MRI scan analysis over a minimum of a 2 year follow-up period showed improvement in Pfirrmann grading; this is suggestive of the reversal of degenerative changes and healing. Whether or not such simplified interventional pain management procedures with MSC withstand the test of time or even replace interbody fusion techniques remains to be seen and should be the subject of innovative research. The authors are keenly aware that our observations only provide low-grade clinical evidence. However, they recognize that every innovation starts with the lowest grade of clinical evidence - Level 5 – clinical observations. Further investigation of this fast-moving field of regenerative medicine applications in interventional and surgical spine care is underway.

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