Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy

A Randomized, Double-Blind, Controlled Study

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Background: There are limited treatment options for tissue restoration and the prevention of degenerative changes in the knee. Stem cells have been a focus of intense preclinical research into tissue regeneration but limited clinical investigation. In a randomized, double-blind, controlled study, the safety of the intra-articular injection of human mesenchymal stem cells into the knee, the ability of mesenchymal stem cells to promote meniscus regeneration following partial meniscectomy, and the effects of mesenchymal stem cells on osteoarthritic changes in the knee were investigated.

Methods: A total of fifty-five patients at seven institutions underwent a partial medial meniscectomy. A single superolateral knee injection was given within seven to ten days after the meniscectomy. Patients were randomized to one of three treatment groups: Group A, in which patients received an injection of 50×10^6 allogeneic mesenchymal stem cells; Group B, 150×10^6 allogeneic mesenchymal stem cells; and the control group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control. Patients were followed to evaluate safety, meniscus regeneration, the overall condition of the knee joint, and clinical outcomes at intervals through two years. Evaluations included sequential magnetic resonance imaging (MRI).

Results: No ectopic tissue formation or clinically important safety issues were identified. There was significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in Group A and 6% in Group B at twelve months post meniscectomy ($p = 0.022$). No patients in the control group met the 15% threshold for increased meniscal volume. Patients with osteoarthritic changes who received mesenchymal stem cells experienced a significant reduction in pain compared with those who received the control, on the basis of visual analog scale assessments.

Conclusions: There was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human mesenchymal stem cells. These results support the study of human mesenchymal stem cells for the apparent knee-tissue regeneration and protective effects.

continued

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More than one million knee arthroscopy procedures are performed annually in the U.S., of which the majority are for surgical repair or partial excision of meniscal tears[1,2]. Unfortunately, the failure rate of approximately 20% to 24% has not substantially changed even with the advent of all-inside surgical techniques[3]. Younger patients with traumatic lesions in the vascular zone of the meniscus, especially those in combination with an anterior cruciate ligament (ACL) tear that undergoes reconstruction, have higher rates of repair and healing, while older patients with isolated meniscal tears have lower rates of repair and healing. With a partial meniscectomy, the deepest radial loss of tissue determines the biomechanical effect. A posterior horn flap that extends in only one zone to within 1 to 2 mm of the periphery is similar biomechanically to a subtotal meniscectomy[4]. Partial meniscectomy is associated with a definitive risk of degeneration that may take years to develop for a neutrally aligned limb with a loss of medial meniscal function, yet this degenerative change may occur only months to a few years following a partial lateral meniscectomy. A partial meniscectomy increases the risk of osteoarthritis at least ten to twentyfold[5,6].

There continues to be strong interest in improving meniscal repair and healing rates to restore meniscal function. The currently available restorative procedures are a meniscal allograft transplantation or a scaffold implantation (not presently available in the U.S.). Meniscal allograft transplantation has good outcomes in younger patients but is complicated by considerations that include sizing, graft degradation, surgical attachment techniques, and concomitant pathologies[7].

Mesenchymal stem cells are cells of mesodermal origin that have the capacity to differentiate into connective tissues, including bone, cartilage, tendon, ligament, and fat[8]. They have demonstrated anti-inflammatory and immunomodulatory effects[9,10]. Several preclinical studies have demonstrated the beneficial role of mesenchymal stem cells in neomeniscal tissue formation and joint preservation[11-15]. Specifically, studies of meniscal defects in various animal models have shown that mesenchymal stem cells administered into the joint adhered to and persisted on the surface of a damaged meniscus, differentiated into meniscal cells, and expressed appropriate extracellular matrix (collagen type I and II), resulting in a regeneration of meniscal tissue, which, with an improved meniscus, ultimately could lead to long-term chondroprotection. Substantial evidence now exists that preparations of allogeneic mesenchymal stem cells do not have adverse immune effects[16,17].

This double-blind, randomized, controlled clinical study examined the effect of a single intra-articular injection of human mesenchymal stem cells compared with that of a vehicle control following partial meniscectomy surgery. The objectives were to evaluate the safety of intra-articular injection of mesenchymal stem cells into the knee, the cells' ability to promote meniscus regeneration following surgery, and their effects on osteoarthritis in the knee joint.

Materials and Methods

Trial Design and Disposition

The trial was a phase I/II, randomized, double-blind, controlled study of mesenchymal stem cells delivered by a single intra-articular injection after partial meniscectomy. Sixty patients who were between the ages of eighteen and sixty years old were randomly assigned to one of three treatment groups at a ratio of 1:1:1. The treatment for Group A was 50 million human mesenchymal stem cells; for Group B, 150 million human mesenchymal stem cells; and for the control group, a vehicle control. Manual randomization was performed with the use of sealed envelopes generated by a centralized scheme.

The trial was conducted in compliance with current Good Clinical Practice (cGCP) standards and in accordance with the principles set forth under the Declaration of Helsinki (1989). The institutional review board at each center approved the protocol, and each study patient signed an institutional review board-approved informed consent form.

To be eligible, patients had to have been a candidate for a partial medial meniscectomy based on magnetic resonance imaging (MRI) at screening and the surgeon's evaluation. The operating surgeon made the final determination of the need for the meniscectomy and the extent of meniscectomy meeting the 50% threshold intraoperatively (the excision of at least 50% of the medial meniscus). All were subtotal meniscectomies. Any previous knee ligament reconstruction needed to have had a stable result. Patients could not have indwelling devices or conditions that would interfere with MRI. Randomization occurred after all eligibility criteria were met and after the partial meniscectomy was performed (see Appendix).

A total of fifty-five patients were treated by seven surgeons at their respective centers: eighteen patients in Group A, eighteen patients in Group B, and nineteen patients in the control group. Eight of the sixty randomized patients discontinued, five of whom discontinued before treatment with the investigational agent. Major follow-up assessments and MRI were conducted at baseline (prior to injection of the investigational agent) and at six weeks, six months, one year, and two years postoperatively (Fig. 1 and Appendix).

Study Treatment

Patients received the investigational agent at the treatment visit seven to ten days after the partial meniscectomy surgery. The treating surgeon delivered the injection into the superolateral aspect of the suprapatellar pouch according to sterile technique. An 18-gauge needle was used to deliver the investigational agent as a bolus injection after a confirmatory aspiration of fluid. The syringe was obscured with colored cellophane wrap to maintain blinding. Following the injection, the knee was passively flexed and extended through a full range of motion five times.

The active investigational agent was a preparation of ex vivo cultured adult human mesenchymal stem cells, hMSCs (Osiris Therapeutics, Columbia, Maryland), derived from bone-marrow aspirates obtained from unrelated donors not human leukocyte antigen (HLA)-matched to recipients. The human mesenchymal stem cells were derived from the bone marrow of donors who were eighteen to thirty years of age and who had been screened and tested according to U.S. Food and Drug Administration (FDA) requirements for blood and tissue-based products. No donors were pooled. The lots were manufactured by a scaled adaptation of the technique according to Good Manufacturing Practices (GMP),

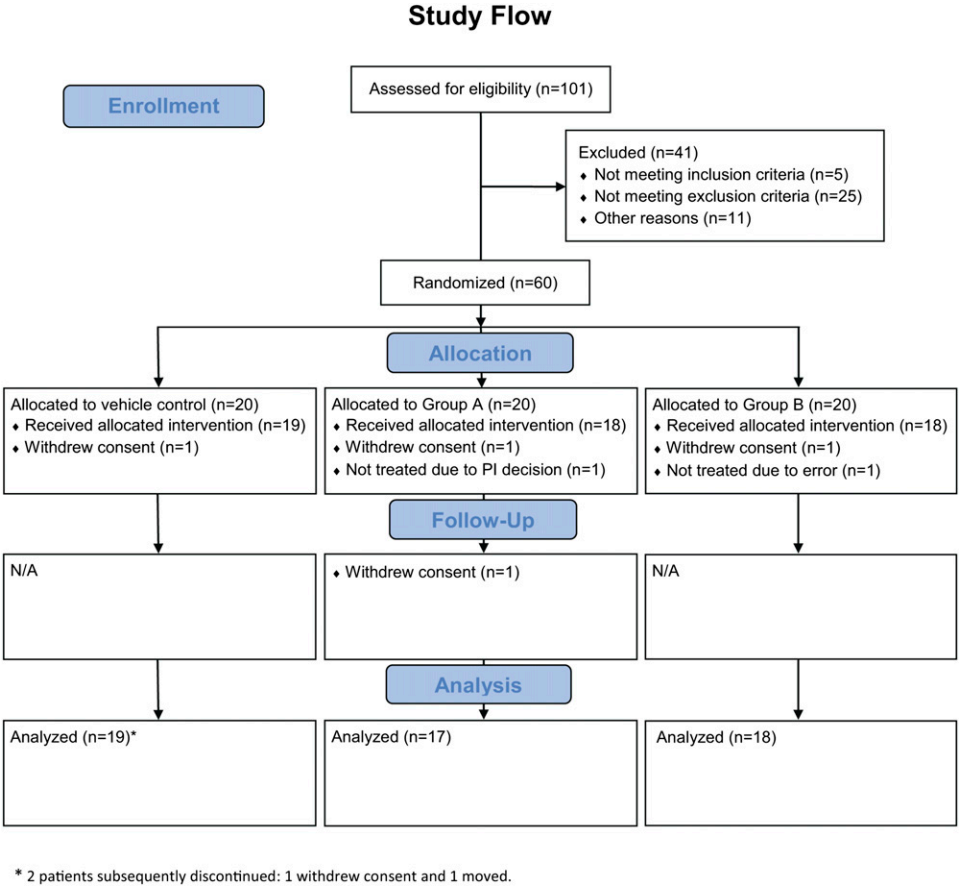

Fig. 1

A CONSORT diagram showing the flow of patients in the study. PI = principal investigator; N/A = not applicable.

as described previously[8,16]. All lots passed established quality-release criteria for viral pathogens, mycoplasma, sterility, endotoxin, cell identity, purity, and viability prior to use. The cells were stored at ≤−135°C until use.

The formulated treatment for injection consisted of 50×10^6 human mesenchymal stem cells (Group A) or 150×10^6 human mesenchymal stem cells (Group B) suspended in 2 mL (20 mg) of sodium hyaluronate (hyaluronic acid/hyaluronan), human serum albumin (1.2%), and PlasmaLyte A to a volume of 5 mL, or the vehicle control (control group). The vehicle control comprised the same sodium hyaluronate solution, without the human mesenchymal stem cells.

Patients were required to avoid strenuous activities or prolonged weight-bearing for forty-eight hours after the study injection and running and/or repetitive-impact activity for six weeks after surgery. For six months after treatment, additional knee injections, oral glucosamine/chondroitin, and oral corticosteroids were not permitted.

Safety

Physicians and other clinical personnel remained blinded to the treatment assignment throughout the study. Safety assessments included an evaluation of adverse events and serious adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Clinical laboratory and urine values, vital signs, and standard physical examination results were recorded and shifts from normal were noted. The knee was examined to inspect for redness, swelling, deformity, abnormal tissue presentation, and/or skin changes. To detect a cell-mediated or humoral immune response, the expression of immune cell markers for T cells, natural killer cells, and B cells in the peripheral blood was measured and shifts from normal were analyzed relative to measurements at preoperative baseline. Safety was monitored continually, and specific assessments were performed at the treatment visit prior to injection and at the time of follow-up visits thereafter. MRI was reviewed for abnormal (ectopic) tissue formation.

Magnetic Resonance Imaging

MRI was performed on a clinical-grade machine (1.5 T for twenty-nine patients and 3.0 T for twenty-six patients) with a transmit/receive, phased-array knee coil. A cartilage-sensitive pulse sequence using moderate echo time and fast-spin-echo techniques was performed, yielding differential contrast between fluid, articular cartilage, and subchondral bone/calcified cartilage.

MRI was used as a preoperative screening measure. MRI was then acquired at the treatment visit at the time of the injection of the investigational agent (baseline, to determine the status of the meniscus after surgery) and at major follow-up visits.

The field of view, matrix, and slice thickness were constant throughout the examination and on subsequent visits. Scans were acquired in the axial plane, the sagittal plane, and the coronal plane. The sagittal-plane scans were aligned parallel to the lateral femoral condyle covering the entire knee. The coronal-plane scans were perpendicular to the lateral femoral condyle and also covered the entire knee.

Computational analysis of meniscal volume was performed by two independent, university-based musculoskeletal radiologists. To ensure blinding in the early stages of the study, random knee images were inserted into the sequence of the analyses. SliceOmatic version 4.3 software (TomoVision, Montreal, Canada) was used to digitize the DICOM (Digital Imaging and Communications in Medicine) images. Images of each 2-mm slice were digitized and the three-dimensional volume reconstructed for each plane of MRI acquisition. To compute the meniscal boundaries of each slice, the outline of the body of the meniscus was determined through

TABLE I Incidence of Adverse Events*

	Control (N = 19)	Group A 50 × 10^6 hMSCs (N = 18)	Group B 150 × 10^6 hMSCs (N = 18)
Total no. of adverse events	118	158	151
No. of patients with ≥1 adverse event (%)	17 (90)	18 (100)	17 (94)
Adverse events by system organ class* *(no. [%])*			
General disorders and administration-site conditions	6 (32)	10 (6)	11 (61)
Infections and infestations	3 (16)	3 (17)	3 (17)
Injury and procedural complications	6 (32)	8 (44)	8 (44)
Investigations	3 (16)	6 (33)	2 (11)
Musculoskeletal and connective tissue disorders	15 (79)	18 (100)	17 (94)
Nervous system disorders	5 (26)	5 (28)	6 (33)

*Data represent adverse events by system organ class (NCI CTCAE) occurring in at least three patients in any arm.

automatic signal analysis with use of threshold segmentation. Then the signal intensity of the border pixels was visually inspected. Each border pixel was individually screened using the threshold segmentation mode. Pixel size was 0.42 × 0.42 mm.

The volume of the meniscus was determined at each of the postoperative time points with the use of volume-analysis postprocessing techniques and compared with the postoperative volume of the meniscal remnant from the zone of resection to quantify meniscal regeneration.

MRIs were assessed for cartilage degeneration with the use of a semiquantitative scoring method, as well as assessed for thickening and sclerosis of subchondral bone, osteophyte formation, and femoral or tibial edema[18].

Patient-Reported Assessments

Patient knee pain was assessed with use of a visual analog scale (VAS) of 0 to 100 mm. The Lysholm knee scale self-assessment was also utilized[19].

Statistical Analysis

Continuous data were described with the use of descriptive statistics: n, mean, standard deviation, median, minimum, and maximum. For each study end point, only observed data were used for analysis and no imputation of missing values was employed. All analyses were conducted with the use of SAS software (SAS Institute, Cary, North Carolina) version 8.2 or higher.

Categorical measures on an ordinal scale were analyzed with use of the Mantel-Haenszel test for general association for pairwise treatment-group comparisons and overall comparisons of the three treatment groups. Categorical measures on a nominal scale were tested on general association between treatment groups and outcomes at each visit with use of the Mantel-Haenszel test for general association. When appropriate, a Fisher exact test was used for nominal outcomes and exact p values of Mantel-Haenszel correlation tests were used for ordinal outcomes.

The sample size was based on the proportion of patients with a >15% improvement in MRI-based meniscal volume from baseline. The study had 90% power to detect a 60% difference between treatment and control with 5% type-I error using a two-sided hypothesis test.

Two-sided tests were used at a type-I error rate of 5% for comparison between any two of the treatment groups or control and overall among the three treatment groups. Paired tests were used for significant changes from baseline for any one of the treatment groups. There was no adjustment for multiple treatment comparisons or testing of multiple study end points in this exploratory study.

The completed population comprised all randomized patients who had the scheduled six-month MRI. The safety population comprised all randomized patients who received the investigational agent.

Source of Funding

This study was funded by Osiris Therapeutics, Columbia, Maryland (ClinicalTrials.gov: NCT00225095).

TABLE II Incidence of Serious Adverse Events

	Control (N = 19)	Group A 50 × 10^6 hMSCs (N = 18)	Group B 150 × 10^6 hMSCs (N = 18)
Acute myocardial infarction	0	1	0
Ileus	0	1	0
Small-intestine obstruction	1	0	0
Femur fracture	0	0	1
Fibula fracture	0	0	1
Hand fracture	1	0	0
Meniscus lesion	0	1	0
Osteoarthritis	0	2	0

TABLE III Shifts in Immunological Parameters from Baseline*

	Vehicle Control (N = 19)			Group A 50 × 10^6 hMSCs (N = 18)			Group B 150 × 10^6 hMSCs (N = 18)		
	Baseline			Baseline			Baseline		
	L	N	H	L	N	H	L	N	H
CD3									
6 wk		1L			1L				
6 mo					1L			1L	
2 yr		2L			1L, 1H				
CD4									
6 wk	1N	1L				2N		1L	
6 mo		1L				2N		1H	
2 yr		1L				2N		1L, 1H	
CD8									
6 wk		1L			1L				
6 mo		1L			1L			1L	
2 yr		1H	1N						
CD56									
6 wk		1L	1N	1N	1L	1N		1L, 1H	1N
6 mo	2N	1L, 1H	1N	1N				1L, 1H	1N
2 yr		1H	1N	1N	1L	2N			1N
CD20									
6 wk	1N		2N			3N			2N
6 mo	1N		2N		1L	3N			3N
2 yr	1N		4N		1H	3N			3N

*L = low, N = normal, and H = high. Only numbers for shifts relative to baseline are shown.

Results

Basic demographic data for the sixty patients randomized are presented in the Appendix. The overall mean age was 46.0 years, and 63% were male. There were no significant differences in baseline characteristics among the cohorts ($p > 0.05$). Only one patient had a prior ACL reconstruction on the study knee. No patients were unblinded prematurely.

Clinical Evaluation

There were no deaths during the study, and no adverse events led to treatment discontinuation or study termination. A total of 427 adverse events were recorded among the fifty-two patients in the safety population (95%) who had at least one adverse event (Table I). Of the total adverse events, 272 were reported as mild, 126 as moderate, twenty-eight as severe, and one as life-threatening (the patient had a heart attack approximately one year after the study injection). The most frequently reported adverse events by system organ class were musculoskeletal and connective tissue disorders (fifty of fifty-five patients, 91%), followed by general disorders and administration-site conditions (twenty-seven of fifty-five, 49%). The most common adverse events by preferred term were arthralgia, joint swelling, joint stiffness, injection-site joint pain, joint effusion, headache, and peripheral edema. Nine serious adverse events occurred in eight patients (Table II) and all were deemed by the blinded investigators as unlikely to have been related to the investigational agent.

There were no trends identified in the shifts in immunological parameters measured—CD3, CD4, CD8, CD56, or CD20 (Table III)—nor were there trends in hematology, blood chemistry, or urine analyses after the injection of the investigational agent. No patient had a clinically significant abnormal hematology laboratory result. One patient with a history of calcium oxalate crystals experienced a clinically abnormal urinalysis result listed as "crystals." The number of patients with shifts in laboratory values from normal at baseline to values outside the normal range or with shifts from normal to abnormal for categorical analyses of urine values was generally low (four or fewer patients per parameter).

There were no major changes in vital signs after injection. There were no notable changes from baseline in the physical examination data. There was no ectopic tissue formation noted from the blinded MRI evaluation.

MRI Evaluation

The patients meeting the predefined criterion of a >15% increase in meniscal volume were determined from the MRI computational analysis. The results of the analysis relative to baseline

TABLE IV MRI Results for Meniscal Volume

	Vehicle Control (N = 19)	Group A 50 × 10^6 hMSCs (N = 17)	Group B 150 × 10^6 hMSCs (N = 18)
Patients with >15% Increase in Meniscus Volume Relative to Baseline			
6 mo			
No. patients (% [95% CI])*	0 (0.0-17.6)	1 (6% [0.1-28.7])	1 (6% [0.1-27.3])
P value†			
Control vs. Group A	0.472		
Control vs. Group B	0.486		
Overall	0.535		
12 mo†			
No. of patients (% [95% CI])*	0 (0.0-17.6)	4 (24% [6.8-49.9])	1 (6% [0.1-27.3])
P value†			
Control vs. Group A	0.040		
Control vs. Group B	0.486		
Overall	0.022		
2 yr§			
No. of patients (% [95% CI])*	0 (0.0-19.5)	3 (18% [4.0-45.6])	0 (0.0-19.5)
P value†			
Control vs. Group A	0.103		
Control vs. Group B	>0.999		
Overall	0.029		

*CI = confidence interval. †P values are for the three pairwise treatment group actual result comparisons and the overall comparison of the three treatment groups with use of the Mantel-Haenszel general association test. ‡One patient in Group A did not undergo MRI at this time point. §Two patients in Group A and one patient in Group B did not undergo MRI at this time point.

(post meniscectomy and prior to the injection of the investigational agent) are shown in Table IV. At the six-month evaluation, an increase in meniscus volume of >15% was observed in two patients, one each in Group A and Group B. At twelve months, four patients in Group A met the threshold of increase in meniscal volume. At two years, three patients in Group A demonstrated an increase in meniscus volume of >15%. At no time point was the criterion of an increase in meniscal volume achieved in any of the patients in the control group. At twelve months, both the control group compared with Group A ($p = 0.040$) and the overall group comparison ($p = 0.022$) were significant in terms of the proportion of patients meeting the criteria of a >15% improvement in MRI-based meniscal volume. At two years, the overall group comparison was significant ($p = 0.029$).

The initial joint evaluation indicated that seven patients in the control group, eleven patients in Group A, and twelve

TABLE V Total Lysholm Knee Scale Scores*

	Vehicle Control (N = 19)	Group A 50 × 10^6 hMSCs (N = 17)	Group B 150 × 10^6 hMSCs (N = 18)
Baseline			
Mean ± SD	62.5 ± 19.41	56.4 ± 23.02	57.7 ± 20.94
Median	68.0	51.0	63.5
Min, max	29.0, 95.0	15.0, 93.0	22.0, 90.0
Change from baseline			
6-mo mean ± SD	31.3 ± 19.50	20.6 ± 33.90	28.1 ± 31.81
1-yr mean ± SD	34.4 ± 19.34	22.9 ± 33.52	34.1 ± 22.02
2-yr mean ± SD	33.8 ± 20.03	31.8 ± 30.68	37.1 ± 31.27

*SD = standard deviation.

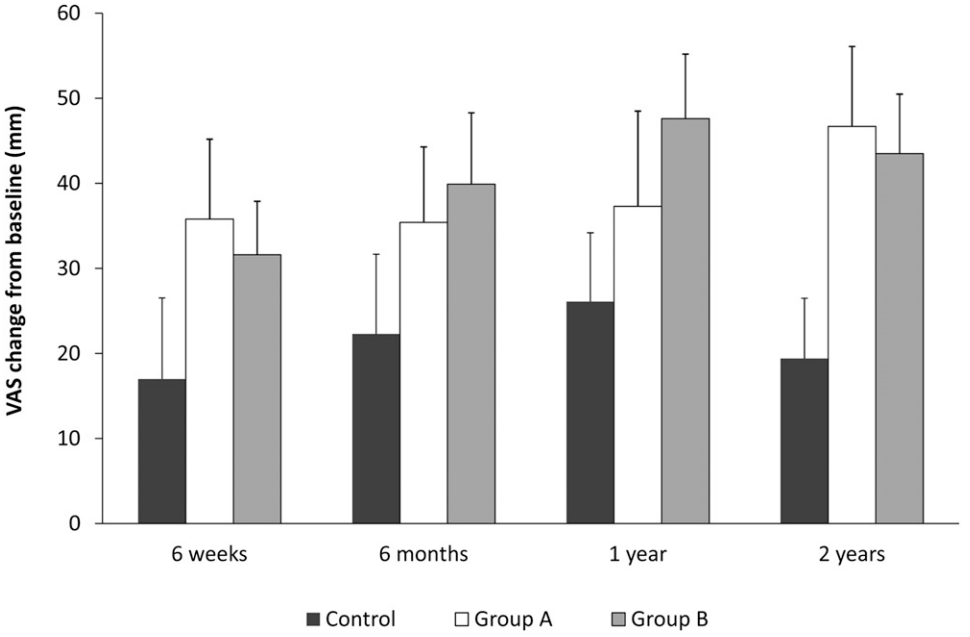

Fig. 2

Improvement in VAS pain scores through two years post meniscectomy surgery in patients with evidence of cartilage degeneration on MRI. The time points at which strong trends or significant differences from the control were observed were at two years for Group A ($p = 0.05$), and at one year ($p = 0.08$) and two years ($p = 0.04$) for Group B. Control = sodium hyaluronate, Group A = 50×10^6 hMSCs, and Group B = 150×10^6 hMSCs. The I bars represent 95% confidence intervals.

patients in Group B had degenerative changes consistent with osteoarthritis. At six months, 82% of the patients overall had no additional signs of degenerative changes, and by one year, the articular cartilage condition was unchanged in 76% of the patients. In Group A, there was evidence of articular cartilage degeneration on the medial femoral condyle in two patients at one year compared with baseline. In Group B, one patient had developed minor degeneration on the medial femoral condyle and lateral tibial plateau, and one patient had minor damage on the medial patella by one year. One subject in the control group had developed moderate articular degeneration on the medial femoral condyle.

Subchondral sclerosis and osteophyte formation were reported in 21% of patients receiving the control, but only 6% of patients treated with the human mesenchymal stem cells.

Patient-Reported Assessments

Knee pain was assessed with use of a 100-mm VAS (see Appendix). Overall, VAS pain scores decreased significantly for patients post surgery compared with baseline values ($p < 0.001$) for all treatment groups. The baseline values were similar among groups (mean, 43.0 mm for the control group, 56.0 mm for Group A, and 43.1 mm for Group B). In patients with osteoarthritic changes at the time of surgery, improvement relative to the vehicle control was observed for both groups (Fig. 2). The average relative improvement was 18.8 mm at six weeks, increasing to 27.3 mm at two years, for Group A. A comparable increase was seen for Group B, which had a relative difference of 14.6 mm at six weeks and 24.1 mm at two years. The time points at which strong trends or significant differences from the control were observed were at two years for Group A ($p = 0.05$) and at one year ($p = 0.08$) and two years ($p = 0.04$) for Group B.

Patients improved in their Lysholm knee scale total scores relative to baseline at all time points ($p \leq 0.03$) (Table V).

Discussion

To our knowledge, this was the first randomized, double-blind, controlled study to evaluate the safety, regenerative effects, and clinical outcomes of human mesenchymal stem cells delivered by intra-articular injection into the human knee. The results demonstrated that high doses of allogeneic mesenchymal stem cells can be safely delivered in a concentrated manner to an enclosed space (knee-joint capsule) without abnormal tissue formation. This finding is consistent with the results of previous studies of the systemic administration of allogeneic mesenchymal stem cells that showed no evidence of ectopic tissue formation on imaging studies[16,17].

Overall, the study injections were well tolerated. There were no adverse events that led to treatment discontinuation or study termination. Many of the listed adverse events are not uncommon following intra-articular injection. Sequential immunologic, hematologic, and urine testing showed no clinically significant trends. A few patients experienced clinically abnormal laboratory results, none of which were considered related to study injection.

The results of this study suggest that mesenchymal stem cells have the potential to improve the overall condition of the

knee joint. Although there is a large body of preclinical research supporting the use of mesenchymal stem cells in the knee, to date, only very limited clinical data are available. There has been some research on the effects on articular cartilage degeneration, but this has predominantly been small, limited case reports or series on the administration of autologous cells from various sources[18]. Here, controlled data in an exploratory study showed that some patients had an increase in meniscal volume, particularly at one year, indicating de novo tissue regeneration. Preclinical studies have suggested that mesenchymal stem cells may promote tissue regeneration through mesenchymal stem cell adherence, production of trophic factors, extracellular matrix deposition, and differentiation into meniscal cells, all of which may contribute to tissue regeneration[11-14,20,21].

A higher proportion of those with osteoarthritic changes experienced a reduction in pain following the treatment with mesenchymal stem cells. The reduction in pain was relative to an "active" control sodium hyaluronate. Hyaluronan itself is a treatment for the pain of osteoarthritis and may have provided some benefit to the patients. The magnitude of effect relative to the active control (hyaluronate) was clinically meaningful. The observed effect on a patient-reported outcome was compelling given that this was a double-blind study, which compensates for the possible bias from knowing that one received "stem cells." The ability to mitigate the impact of the removal of meniscal tissue, which serves to protect the joint, particularly in patients who already have some signs of osteoarthritic changes and may be more at risk to further changes, is a unique possibility that is worth further investigation in larger studies. The Lysholm knee scale score failed to show a similar effect between the three treatment groups.

Limitations of the study included challenges encountered with quantitative MRI analysis of the knee. There were difficulties with the consistency of MRI scans from different centers and from visit to visit, and also with the edge-detection evaluation. Further work is needed to validate the quantitative assessment of meniscal volumes and the effect of 1.5-T or 3.0-T MRI. The evaluation of meniscal volumes was initiated in this study in an effort to demonstrate the mechanism of the protective effects of human mesenchymal stem cells in the knee. However, regulatory requirements will necessitate a focus on patient-reported outcomes in future studies. Another limitation was the difference in the distribution of the presence of osteoarthritis across the groups, as this was not controlled during enrollment. Additional studies could ensure balance of this factor among the groups.

This study provided, to our knowledge, the first controlled data on the results of injecting allogeneic mesenchymal stem cells into the knee in humans and supports the safety of intra-articular injection of human mesenchymal stem cells. This study investigated the single administration of stem cells at two dose levels. The data do not suggest that there was increased benefit from the higher dose. Whether providing additional injections influences the effect on pain, meniscus regeneration, or osteoarthritis remains to be evaluated.

Appendix

(eA) Tables showing the study's inclusion and exclusion criteria, patient demographic data and baseline characteristics by group, and absolute improvement in VAS scores overall and among patients with changes consistent with osteoarthritis are available with the online version of this article as a data supplement at jbjs.org. ■

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