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Treatment of Lateral Epicondylosis Using Allogeneic Adipose-Derived Mesenchymal Stem Cells: A Pilot Study

SANG YOON LEE,[a] WON KIM,[b] CHAIYOUNG LIM,[c] SUN G. CHUNG[c,d,e]

Key Words. Mesenchymal stem cell transplantation • Allograft • Tennis elbow • Tendinopathy • Adipose tissue

[a]Department of Physical Medicine & Rehabilitation, Chung-Ang University College of Medicine, Seoul, South Korea; [b]Department of Rehabilitation Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [c]Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, South Korea; [d]Institute of Aging, Medical Research Center, Seoul National University, Seoul, South Korea; and [e]Rheumatism Research Institute, Medical Research Center, Seoul National University, Seoul, South Korea

Correspondence: Sun G. Chung, Ph.D., M.D., Department of Rehabilitation Medicine, Seoul National University Hospital, 101 Daehang-ro, Jongno-gu, Seoul 110-744, South Korea. Telephone: +82-2-2072-2560; Fax: +82-2-745-2560; e-mail: suncg@snu.ac.kr

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ABSTRACT

Mesenchymal stem cell therapy is a novel regenerative approach for treating tendinopathy. Here, we evaluated the safety and efficacy of allogeneic adipose-derived mesenchymal stem cells (*allo*-ASC) in treating lateral epicondylosis (LE). Under ultrasound guidance, *allo*-ASCs mixed with fibrin glue were injected into the hypoechoic common extensor tendon lesions of 12 participants with chronic LE; 6 subjects each were administered 10^6 or 10^7 cells in 1 ml. Safety was evaluated at day 3 and weeks 2, 6, 12, 26, and 52 post-injection. Efficacy was assessed by measuring patients' visual analog scale (VAS) score for elbow pain, modified Mayo clinic performance index for the elbow, and by evaluating longitudinal and transverse ultrasound images of tendon defect areas after 6, 12, 26, and 52 weeks. No significant adverse effects of *allo*-ASC injection were observed through 52 weeks of follow-up. From baseline through 52 weeks of periodic follow-up, VAS scores progressively decreased from 66.8 ± 14.5 mm to 14.8 ± 13.1 mm and elbow performance scores improved from 64.0 ± 13.5 to 90.6 ± 5.8. Tendon defects also significantly decreased through this period. *Allo*-ASC therapy was thus safe and effective in improving elbow pain, performance, and structural defects for 52 weeks. This clinical study is the first to reveal therapeutic value of mesenchymal stem cell injection for treating chronic tendinopathy. STEM CELLS *2015; 00:000–000*

SIGNIFICANCE STATEMENT

Clinical use of mesenchymal stem cells in the treatment of tendinopathy has not been well studied because it may be related to the invasive procedures required to obtain autologous stem cells. Allogeneic stem cells may be an optimal treatment option for tendinopathy, if safety and efficacy can be conclusively demonstrated. Here, we evaluated the safety and efficacy of allogeneic adipose-derived mesenchymal stem cells in treating chronic lateral epicondylosis of 12 participants. No significant adverse effects of allogeneic stem cells were observed through 52 weeks of follow-up. Elbow pain, performance scores, and tendon defects area measured by ultrasound improved through this period. This clinical study is the first to reveal therapeutic value of mesenchymal stem cell injection for treating chronic tendinopathy.

INTRODUCTION

Lateral epicondylosis (LE) originating from degenerative conditions in wrist extensor tendons [1] is the most common elbow disease with a prevalence of 1%–3% in the general population [2]. Although 83% of individuals with LE lasting more than 6 weeks spontaneously recover in 1 year without intervention [3], the remaining 17% are difficult to manage successfully [4], and unresolved symptoms lead to chronic disease [5]. In patients with chronic LE, conservative approaches for managing symptoms, including anti-inflammatory drugs, physiotherapy [6, 7], brace [8], and therapeutic exercise [9] have produced unsatisfactory outcomes [10]. Several injection therapies have been investigated as means to overcome the difficulty in treating LE clinically. While corticosteroid injection has been widely used for short-term pain relief, the effectiveness of the treatment is transient [3, 4]. Furthermore, corticosteroids suppress the cellular activity of human tenocytes and collagen synthesis [11], thereby weakening tendons and increasing the risk of rupture [12, 13].

Regenerative therapy with several chemical or biological materials has been used to promote the healing of injured tendon tissues. Prolotherapy with dextrose solutions [14, 15],

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autologous whole blood injection [16], and platelet-rich plasma with an increased concentration of autologous platelets [17–21] are regenerative medicine options for LE. However, limited evidence supports the efficacy of these treatment approaches [22], and a recent systematic review reported strong evidence against the effectiveness of platelet-rich plasma injection for treating chronic LE [23].

Mesenchymal stem cell (MSC) injection is emerging as a novel regenerative therapy for treating tendinopathy. MSC therapy for tendon injury has been well investigated in the field of veterinary medicine [24]. When 113 racing horses with overstrain injury of the superficial digital flexor tendon were treated with autologous bone marrow-derived MSCs, a minimum 2-year follow-up showed lower reinjury rates and a higher percentage of horses returning to racing than with alternative treatments [25]. Experimental rat [26, 27] and rabbit [28, 29] models also showed benefits of MSC therapy at the mechanical, histological, and molecular levels.

Nevertheless, the clinical use of MSCs in the treatment of tendinopathy has not been well studied. While one group has reported the efficacy of autologous skin-derived tenocyte-like cells in treating LE [30] and patellar tendinopathy [31], to our knowledge, no one has performed a similar study using stem cells. The paucity of clinical research and application may be related to the invasive procedures required to obtain autologous MSCs, regardless of cell origin [32], which imposes inordinate discomfort and risks relative to the nonfatal condition of tendinopathy as a minor musculoskeletal ailment. Given this consideration, transplantation of allogeneic MSCs may be an optimal treatment option for tendinopathy, if safety and efficacy can be conclusively demonstrated.

Based on systematic reviews published several years after infusing allogeneic MSCs [33], safety concerns related to their systemic injection have begun to subside in the cardiovascular [34] and hematological [35, 36] fields. Locally injecting allogeneic MSCs should be safer than injecting cells systemically, and this approach has been safe and beneficial in treating horses for flexor tendonitis with a 24-month observation period [37]. Moreover, a multicenter clinical trial recently reported that allogeneic MSC injection was safe and beneficial in treating perianal fistula in Crohn's disease with a 24-week follow-up period [38]. In light of these findings, we considered whether the success of allogeneic stem cells used to treat perianal fistula could be extrapolated to other soft tissue ailments, such as tendinopathy, especially with the advantages of being readily available and not requiring invasive procedures.

We aimed to evaluate the safety and efficacy of allogeneic adipose-derived mesenchymal stem cell (*allo*-ASC) injection for the treatment of human tendinopathy. The safety and efficacy (measured as improvements in elbow pain, performance scores, and structural defects detected by ultrasonography) of *allo*-ASC injection for chronic and intractable LE were investigated more than a 52-week period. Dose-dependent responses were also evaluated using two different cell concentrations.

Materials and Methods

Participants

Consecutive adult subjects (all more than 19 years old) with chronic and intractable LE were recruited for this study. After LE was clinically diagnosed by patient history and physical examination (pain and focal point tenderness at the lateral epicondyle), LE was confirmed by ultrasonographic detection of defects in the common extensor origin (CEO) tendon. All participants had been suffering from lateral elbow pain for at least 6 months and were treated, without success, by conventional treatments, including physical therapy, oral medication, prolotherapy, and steroid injection [39]. Exclusion criteria included a history of any injection therapy during the past 6 weeks; lateral elbow pain from other musculoskeletal diseases (such as degenerative arthritis, rheumatoid arthritis, synovitis, radial nerve entrapment, and fibromyalgia); an allergic or hypersensitive reaction to bovine-derived proteins of fibrin glue; an acute medical illness or bleeding tendency; women of childbearing age who were unwilling to use barrier contraceptive methods, breastfeeding, or pregnant; participation in any other clinical trials within the month prior to the screening test; and participation in any previous clinical trial involving stem cell administration.

Study Design

This open-label study was conducted at a university hospital in Seoul, Korea to determine the safety and efficacy of two different doses of *allo*-ASC for treatment of LE. The study was initiated in May 2013 and was completed in September 2014. Written informed consent was provided by all participants before joining the clinical study. Eligible subjects were enrolled based on the inclusion and exclusion criteria described above.

To test the safety of *allo*-ASC, a conventional 3 + 3 cohort expansion design [40] was used. First, 10^6 *allo*-ASCs in 1 ml were injected into three consecutive participants, and safety was subsequently assessed after 2 weeks. By design, if one or fewer participants reported an adverse event (AE) with grade 3 or higher severity according to the World Health Organization (WHO) recommendations for grading acute and subacute toxicity [41] outlined in the "Assessments" section, then three more participants were enrolled to receive the same dosage. At 2 weeks after the sixth participant's injection, the decision to enroll three more participants for high-dose treatment (10^7 cells in 1 ml) was made if the same kind of AE with grade 3 or higher severity was not observed in two or more of the six participants receiving 10^6 cells in 1 ml. Three more subjects were enrolled for the high dose using the same protocol as for the low-dose group. Completion of recruitment as planned resulted in six participants each in the low-dose group (group 1) and high-dose group (group 2), as shown in Figure 1.

For safety and efficacy analyses, all subjects were monitored at days 0 and 3, weeks 2, 6, 12, 26, and 52 post-injection. If any health problems arose, including elbow joint pain, they were offered counseling by one of the authors as an unscheduled visit. During this period, all participants were asked not to take anti-inflammatory medications or other injection therapies for LE that could confound the influence of *allo*-ASC treatment. Symptomatic physical therapy was allowed if needed. Acetaminophen and tramadol were the only drugs allowed for treating pain that could not be controlled by conservative treatments. For any drugs taken, the identity, dosage, frequency, and duration were recorded at all follow-up visits. This study was conducted according to Good Clinical Practice guidelines and the principles set out in the Declaration of Helsinki. The study protocol (ClinicalTrials.gov trial number: NCT01856140) and the

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informed consent form were approved by institutional review board (IRB No. 1203-029-400) of our hospital and the Korean Ministry of Food and Drug Safety.

Stem Cell Preparations

Allo-ASCs were isolated from lipoaspirates of human subcutaneous fat tissue obtained from healthy donors who provided informed consent. Donor suitability assessment was performed in accordance with the Guideline on the Requirements for Quality Dossier of Biological Products in Clinical Trials of the Korean Ministry of Food and Drug Safety. Preparation of stem cells from adipose tissues was performed as described previously [32]. The lipoaspirates were washed with phosphate buffered saline and digested in an equal volume of phosphate buffered saline containing 1% bovine serum albumin and 0.025% collagenase type I (Invitrogen, Gaithersburg, MD; http://www.lifetechnologies.com) for 80 minutes at 37°C with intermittent shaking. The isolated stromal vascular fraction was cultured in Dulbecco's modified Eagle's medium (Invitrogen, Gaithersburg, MD; http://www.lifetechnologies.com) that was supplemented with 10% fetal bovine serum (HyClone, Logan, UT; https://promo.gelifesciences.com/gl/hyclone) and 1 ng/ml human basic-fibroblast growth factor to obtain a sufficient number of cells for injection. After harvesting cells by trypsinization, the cells were suspended in Dulbecco's modified Eagle's medium and packaged into single-use vials. *Allo*-ASCs were manufactured using an ASC bank which was established with allogeneic subcutaneous adipose tissues harvested from a healthy donor. As the batch size of the ASC bank from one donor is at least more than 50, the ASCs at passage 3 to passage 4 obtained from one healthy donor were used for this clinical trial. The manufacturing procedure was performed according to the Good Manufacturing Practices authorized by the Korean Ministry of Food and Drug Safety. For lot-release testing, *allo*-ASCs were assessed for cell appearance, viability, identification, purity, content, and potency. The potency was assessed as a viable cell counting. *Allo*-ASCs are known to have diverse biological functions including self-differentiation potential, anti-inflammatory effect, and various growth factor-releasing effect resulting in promoting wound healing and tissue regeneration not by the one of specific mechanisms. In this regard, total amount of viable cells that could exert their biological function was determined by a reasonable potency testing item. Although there is a common limitation of cell therapy product as a personalized medicine for individual patient, we have thoroughly tested in the process of ASC bank to evaluate MSC characteristics such as self-renewal, cell morphology, doubling time, karyotype, cell surface markers, and biological function which includes growth factor releasing and immune suppressive activity to overcome it. Only ASCs met the all testing requirements including test items mentioned above are banked after culturing. All these procedure follows the "Cell Bank Process" which is a standard operating procedure that outlines how to establish cell banking system. The minimum criteria for release were 80% cell viability and less than 1% of CD45-positive cells (a measure of purity). In addition, *allo*-ASCs were screened for contamination with adventitious agents, mycoplasma, bacteria, fungi, and viruses 3 days before packaging to comply with the recommendation of "Guidance on specifications and test methods for cell therapy products" from Korean Food and Drug Administration. Sterility test was performed once more with the sampled final product after packaging.

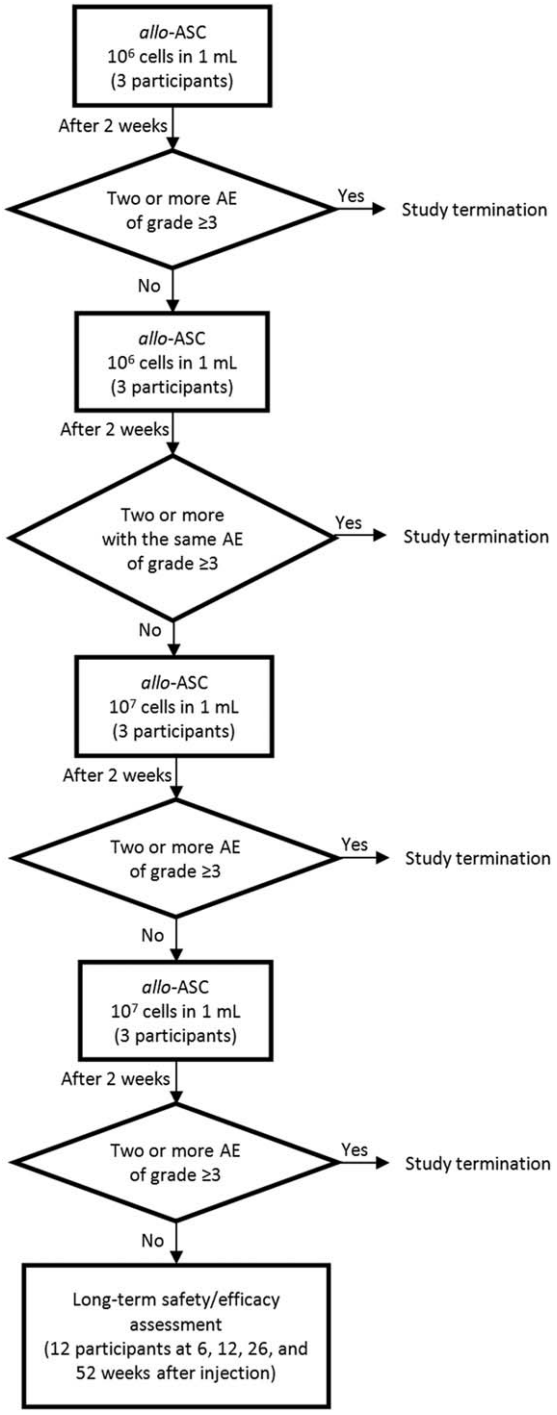

Figure 1. Flow diagram. Schematic representation of the study design, with the conventional 3 + 3 cohort expansion design. Abbreviations: AE, adverse event; allo-ASC, allogeneic adipose-derived mesenchymal stem cells.

Cell Injections

The *allo*-ASCs (Anterogen, Seoul, Korea; http://anterogen.com/main/en) were injected at the largest hypoechoic lesion of the CEO tendon under ultrasonographic guidance. All injections were conducted by a standardized protocol by the

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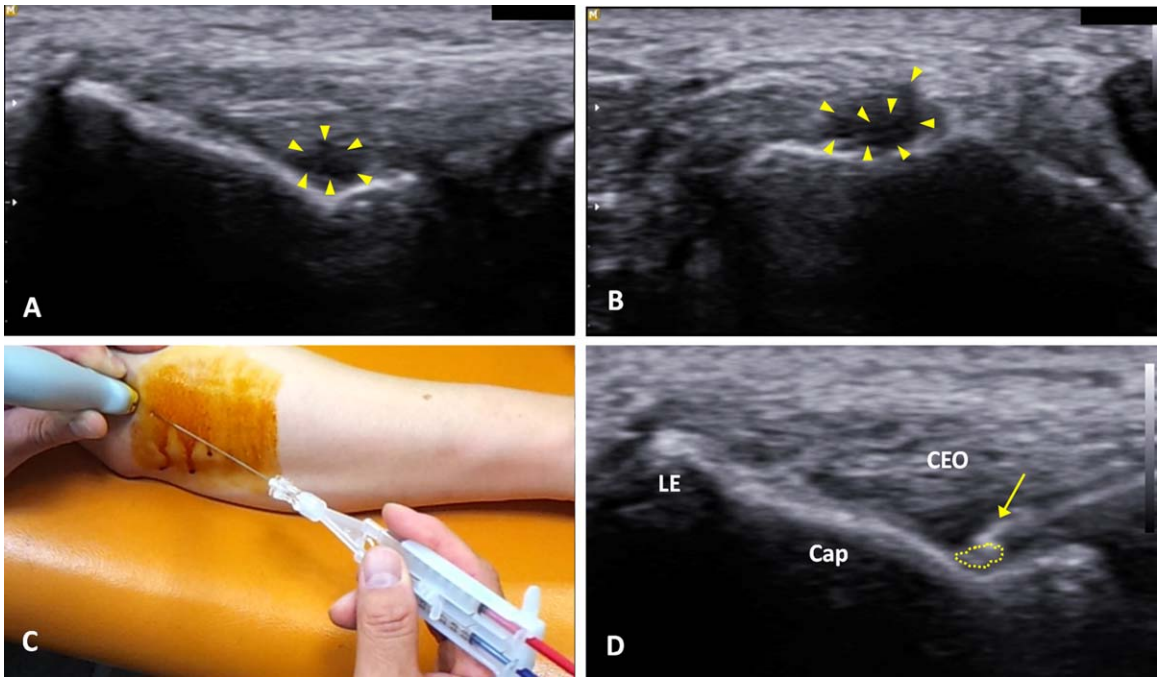

Figure 2. Injection Procedure. Typical defects, the area of fibril discontinuity marked by yellow arrowheads, of the common extensor origin tendon viewed by ultrasonographic imaging of longitudinal **(A)** and transverse **(B)** axes of a subject is shown. Gross photography **(C)** and ultrasonographic image **(D)** of ultrasonography-guided needle insertion (yellow arrow) and inoculation of allo-ASC with fibrin glue (yellow dotted ellipse) into the defect in the common extensor tendon origin on the lateral epicondyle (Supporting Information videos 1 and 2). Abbreviations: Cap, capitellum; CEO, common extensor tendon origin; LE, lateral epicondyle.

senior author (S.G.C.), as described below. Participants assumed a supine position with 30° elbow flexion and full forearm pronation. A dual-syringe injection system (Greenplast kit; Green cross, Seoul, Korea; http://www.greencross.com/eng/main.do) with 22-gauge needles was loaded with 0.5 ml thrombin mixed with 10^6 or 10^7 of *allo*-ASCs in the first syringe and 0.5 ml fibrinogen in the other syringe. When *allo*-ASCs were inoculated in the lesion, thrombin with fibrinogen was used to convert soluble fibrinogen into insoluble fibrin clot rapidly so that ASCs could be trapped within fibrin matrix, an excellent biomaterial to support cell adhesion, for a longer time after injection rather than diffused out. A total volume of 1 ml of this mixture of *allo*-ASCs and fibrin glue was injected into the intratendinous defect of the CEO (Fig. 2). The dose of *allo*-ASCs was predetermined according to the aforementioned recruitment design. After the largest hypoechoic area of CEO tendon which is located deep to the brachioradialis muscle and superficial to the radio-capitellar joint and inserts on the lateral epicondyle was identified in the longitudinal ultrasound view by placing the ultrasound transducer in line with the forearm, a wide area of the skin distal to the transducer was thoroughly disinfected by betadine solution. To prevent injecting air trapped in the needle and injection system, the plunger was depressed to dispel a minimal amount of the injectate out into the air. The needle was inserted into the largest hypoechoic lesion of the CEO tendon under ultrasound guidance (Accuvix V20; Samsung Medison, Seoul, Korea; http://www.samsungmedison.com/) by piercing the skin approximately 1 cm distal to the transducer and penetrating the tendon substance (Supporting Information video clip 1 and 2). The needle insertion procedure was performed as swiftly as possible to prevent clogging of the lumen with fibrin clots.

Assessments

Safety evaluations included AEs based on local tolerances (e.g., pain, swelling, redness, heat, itching, skin change, and any regional discomfort at the injection site); any newly detected ultrasonographic abnormalities around the injected elbow joint; systemic tolerances which were determined by toxic responses with grade 3 or higher [42] using WHO recommendations for grading of acute and subacute toxic effects; immunologic rejection response using the ratio of CD4-positive to CD8-positive T cells (reference value: 0.8–4.2); and laboratory toxicity measured by serum and urine tests including complete blood count with erythrocyte sedimentation rate, admission panel (serum calcium, phosphorus, glucose, BUN/creatinine, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase/alanine transaminase), electrolyte panel (serum sodium, potassium, chloride, and total CO_2), serum hs-CRP quantitation, urinalysis, and urine microscopy test. All safety assessments were thoroughly investigated at days 0 and 3, weeks 2, 6, 12, and 52 after *allo*-ASC injection.

The primary outcome to evaluate efficacy was the 100-mm visual analog scale (VAS) for elbow pain (0, no pain; 100, worst pain possible) during activity. Secondary outcomes included performance tests using the modified mayo elbow performance index (MEPI) and the largest defect area of CEO tendon. The MEPI measures pain, motion, stability, and daily functions. The best MEPI is 100, with the pain score carrying the most weight (45 out of 100 points) [21]. The daily function score comprises five questionnaires regarding daily tasks such as combing one's hair, eating, hygiene, dressing, and putting on shoes and socks [43]. The MEPI has been used as a valid and reliable means to evaluate functional improvements of the elbow joint after therapy [44, 45].

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Defect areas were measured as the largest defect of the CEO tendon in two orthogonal ultrasonographic views (longitudinal and transverse) by two blinded authors (S.Y.L. and C.L.), who each have more than 5 years of experience performing musculoskeletal ultrasounds. To improve the reliability of repeated ultrasonographic measurements, a strict assessment protocol was set up to standardize ultrasound image acquisition. The protocol was devised to acquire ultrasound images of the largest hypoechoic defect in CEO with consistent representation of underlying bony boundaries. With the patient in supine position with the elbow in 30° flexion and full pronation, for the longitudinal view, the cephalic end of the ultrasound transducer was placed on the lateral epicondyle and the long axis of the transducer was aligned with the long axis of the radius. For consistency in each follow-up examination, the alignment of the transducer and radius was achieved by visualizing the bony contours of the smooth down-sloping epicondyle, flat capitellum, and curved radial head in the same view (Fig. 2D). Maintaining the same relative position between the transducer and forearm by avoiding rocking or tilting in any axes, multiple cross-sectional images covering the whole width of the tendon were saved by shifting the transducer medio-laterally by approximately 2 mm at a time [30]. For the transverse view of the tendon, the transducer was placed on the proximal forearm just distal to the radial head, aligning the long axis of the transducer perpendicular to the long axis of the forearm. Viewing the round radius at the horizontal center, the transducer was also shifted proximally by approximately 2 mm without changing orientation, which showed the proximal radius, radial head, joint capsule, distal epicondyle, and prominence of the lateral epicondyle sequentially. Multiple images were saved after the transducer passed the radial head until it slid over the prominence. Because subtle rocking or tilting of the transducer was unavoidable albeit strict manual control, acquiring multiple cross-sectional images in the longitudinal and transverse views were repeated three times.

All ultrasonographic images were obtained by the senior author (S.G.C.), who had more than 10 years of experience in musculoskeletal ultrasound, using a linear 5–13 MHz transducer (Medison, Seoul, Korea) and applying an ultrasound image depth of 2 cm, 50% of gain, set with 12.3 MHz, and neutral (in the middle) time gain compensation for all depths. Saved images were transferred to a picture archiving and communication system as Digital Imaging and Communications in Medicine files, which were exported as Tiff format images for postprocessing. Exported ultrasound image files of each participant were saved in different folders based on each time point when they were achieved such as days 0 and weeks 2, 6, 12, and 52 after *allo*-ASC injection. One of the coauthors (W.K.), being blind to the time points of image achievement, selected one image showing the largest defect for each longitudinal and transverse view at each time point, which resulted in five longitudinal and five transverse images per participant. A total of 120 image files with coded filenames for blinding purpose were pooled together in one folder. Manual measurements were conducted by tracking the perimeter of a defect using ImageJ 1.48 software (National Institutes of Health, http://imagej.nih.gov/ij/) and were repeated three times by each of two examiners in random order to ensure the reliability of the method (Fig. 3). Six measurements were averaged to generate representative data. All the efficacy evaluations were performed at day 0 and 6, 12, 26, and 52 weeks following the *allo*-ASC injections.

Statistical Analysis

Intra-group temporal changes in VAS scores, MEPI, and ultrasonographic defect areas were analyzed by the Friedman test. Wilcoxon signed-rank test with a post hoc Bonferroni correction was used to compare outcomes obtained at follow-up visits to those obtained at day 0. Mann-Whitney *U* tests were used to compare changes in elbow pain, MEPI, and defect areas between groups, relative to baselines values. Cronbach's alpha test was used to verify the reliability of defect area measurements between two ultrasonographers analyzed in three different random orders. PASW Statistics 18 (SPSS, Inc., Chicago, IL) was used for all analyses. p values $<.05$ were considered statistically significant.

Results

Study Population

After screening 14 candidates, 12 subjects were enrolled into the study and injected with *allo*-ASCs. Two of the 14 candidates were not enrolled because they did not provide informed consent and declined to participate in the study. All 12 enrolled participants completed the 52-week post-treatment observation period. Seven participants (58%) were female. The mean age of the study participants was 51.8 ± 9.5 years, and the average duration of LE symptoms before entering this study was 33.0 ± 27.4 months. At baseline, the mean VAS score was 66.8 ± 14.6 mm and the mean MEPI was 64.0 ± 13.5. The average area of the largest tendon defects was 6.46 ± 3.37 mm^2 in the longitudinal axis and 8.14 ± 3.99 mm^2 in the transverse axis. There were no significant differences in age, disease duration, VAS scores, MEPI, or defect areas between groups 1 and 2 (Table 1).

Safety of allo-ASC Injection

No serious adverse effects following *allo*-ASC injection were observed during the 52-week observation period in any of the 12 study participants. Although mild swelling was seen at the injection site in six participants (three in group 1 and three in group 2) within 48 hours after injection, the regional swelling subsided spontaneously (without any treatment) within 2 weeks. A minor degree of elbow joint effusion was detected by ultrasonography in two participants of group 2 at the 2-week follow-up, which was not clinically significant and spontaneously resolved in 1 month. Another subject suffered delayed elbow pain (7 weeks post-injection) after performing self-strengthening exercise including push-ups. After resting and taking rescue analgesics (37.5 mg tramadol and 325 mg acetaminophen per day) for a month, the symptom subsided without recurring. No immunologic rejection responses were detected in any of the subjects, based on the ratio of CD4-positive to CD8-positive T cells.

Pain Relief After allo-ASC Injection

Elbow pain during activity was significantly decreased throughout the observation period ($p < .001$). Compared to VAS scores at day 0 (66.8 ± 14.6 mm), VAS scores 6 weeks post-injection

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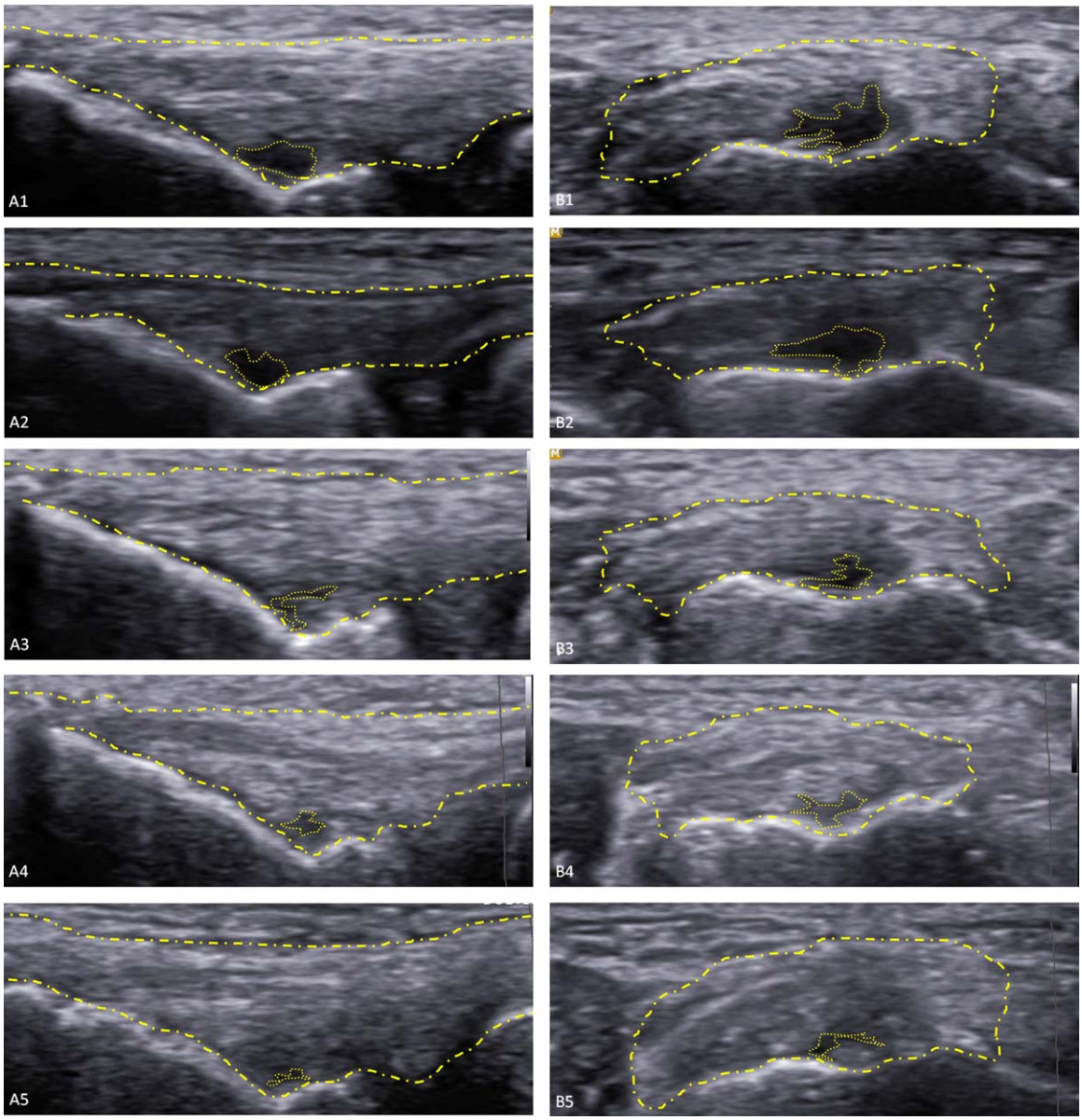

Figure 3. Changes of Defect. Typical serial ultrasonographic images of the largest hypoechoic lesion of longitudinal (left column) and transverse (right column) axes in a subject (**A1/B1**: day 0, **A2/B2**: 6 weeks, **A3/B3**: 12 weeks, **A4/B4**: 26 weeks, and **A5/B5**: 52 weeks after injection). Yellow dash-dot lines and dotted polygons represent the common extensor origin tendon and the defect of the tendon, respectively.

(42.1 ± 23.2 mm; $p = .004$) were significantly lower, and the effect was maintained 12 weeks (31.1 ± 20.6 mm; $p = .002$), 26 weeks (15.3 ± 13.7 mm; $p = .002$), and 52 weeks (14.8 ± 13.1 mm; $p = .002$) post-injection. VAS scores 26 and 52 weeks after injection were also significantly lower than those at 6 weeks ($p = .006$ and $p = .008$, respectively) and 12 weeks ($p = .013$ and $p = .034$, respectively). Even though group 2 tended to show more rapid pain improvement than group 1 from day 0 through 26 weeks, no significant differences were observed in VAS scores between the two groups at any of the follow-up visits (Fig. 4A).

Performance Improvement After allo-ASC Injection

MEPI was significantly increased throughout the observation period ($p < .001$). By comparison with MEPI at day 0 (64.0 ± 13.5), elbow performance scores were significantly improved at 6 weeks (87.1 ± 11.6; $p = .002$), 12 weeks (89.2 ± 6.8; $p = .002$), 26 weeks (92.1 ± 6.1; $p = .002$), and 52 weeks (90.6 ± 5.8; $p = .002$). However, no additional significant improvements were observed beyond the 6-week follow up visit after injection. Changes in MEPI were not different between the two dosage groups throughout the duration of the study (Fig. 4B).

Structural Healing by Ultrasonography After allo-ASC Injection

The reliability test of six measurements of each defect in three different random orders by two blinded evaluators resulted in a Cronbach's alpha value of 0.848. The areas of the largest hypoechoic lesions in the CEO tendon observed by ultrasonography were significantly decreased in both the longitudinal ($p < .001$) and transverse ($p < .001$) axes (Fig. 3). Compared with defect areas observed along the longitudinal

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Table 1. Baseline demographic and clinical data of two groups

	Group 1 ($n = 6$)	Group 2 ($n = 6$)	p-Value[a]
Age (years)	53.2 ± 8.3	50.5 ± 11.1	.688
Sex (n)	Male 3: Female 3	Male 2: Female 4	–
Body mass index (kg/m^2)	25.2 ± 3.0	23.7 ± 3.1	.229
Symptom side (n)	Right 4: Left 2	Right 3: Left 3	–
Duration of symptom (months)	22.8 ± 13.2	43.2 ± 35.1	.294
Elbow pain during activity (VAS, mm)	69.5 ± 19.9	64.2 ± 0.75	.377
Performance score (MEPI)	57.9 ± 15.0	70.0 ± 9.2	.227
Defect area of tendon (longitudinal, mm^2)	4.84 ± 1.87	8.09 ± 3.90	.180
Defect area of tendon (transverse, mm^2)	8.49 ± 4.57	7.78 ± 3.71	1.000

[a]p-Value by Mann-Whitney U test.
Abbreviations: MEPI, modified mayo elbow performance index; VAS, visual analog scale.

axis at day 0 (6.46 ± 3.37 mm^2), those at 26 weeks (2.34 ± 1.42 mm^2; $p = .002$) and 52 weeks (3.06 ± 1.32 mm^2; $p = .003$) were significantly smaller (Fig. 4C). Compared with defect areas of the transverse axes at day 0 (8.14 ± 3.99 mm^2), those at 26 weeks (3.36 ± 1.94 mm^2; $p = .002$) and 52 weeks (4.31 ± 2.10 mm^2; $p = .015$) were also significantly smaller (Fig. 4D). Changes in defect areas were not different at any follow-up visit between two groups.

Discussion

Twelve consecutive participants with chronic, recurrent, and intractable LE were enrolled in this study for *allo*-ASC injection (either 10^6 or 10^7 cells in 1 ml) under ultrasound guidance at the largest hypoechoic lesion of the common extensor tendon. All participants were observed at days 0 and 3, weeks 2, 6, 12, 26, and 52 post-injection of the *allo*-ASCs to investigate the treatment safety and efficacy. There were no serious or clinically significant AEs in any of the participants during the 52-week follow-up period. Elbow pain progressively decreased over time for the entire 52-week follow-up, while elbow performance plateaued after 6 weeks. Ultrasonographic structural defects of the target tendons also decreased in both longitudinal and transverse views after 26 weeks. To our knowledge, this is the first clinical report to

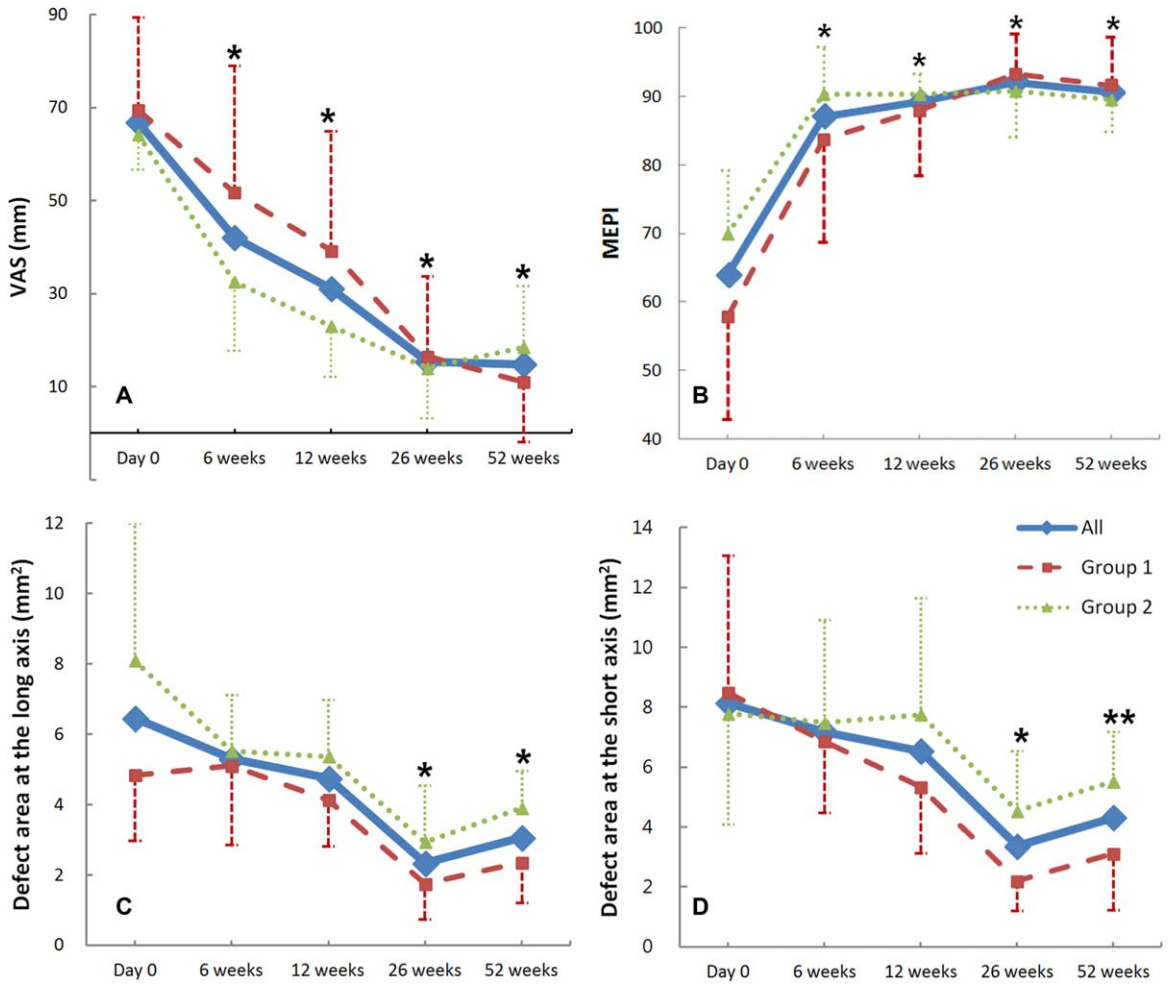

Figure 4. Outcome Measures. **(A)**: Course of VAS pain scores, **(B)** modified MEPI, and the largest hypoechoic lesion area of common extensor tendon origin by ultrasonographic images of both the **(C)** longitudinal and **(D)** transverse axes across the assessment points. Error bars represent 95% confidence intervals for each group. *, p-value < .01; **, p-value < .05 by Wilcoxon signed rank test (compared with the status at day 0 of total participants). Abbreviations: MEPI, mayo elbow performance index; VAS, visual analog scale.

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reveal the safety and efficacy of local MSC injection for the treatment of tendinopathy.

Safety Concerns Regarding MSCs and allo-MSCs

One of the longstanding concerns regarding adverse reactions to MSCs is the potential for carcinogenesis. Rubio et al. reported the first study [46] demonstrating that cellular transformation may occur in human adult MSCs. After long-term in vitro culture and proliferation of MSCs, they underwent spontaneous carcinogenic transformation. However, the authors retracted this article 5 years after its publication, citing probably cross-contamination artifacts and an inability to reproduce their own findings [47]. When Klopp et al. compared studies reporting that MSCs either promote or inhibit tumor growth, they found no evidence of MSC-related tumor growth in more than 1,000 patients treated for various diseases [48]. Furthermore, the authors pointed out several methodological errors in the in vivo studies discussed, which might have promoted tumor growth by the MSCs. Therefore, the carcinogenic potential of MSCs may not be as high as previously thought.

Although allogeneic MSCs offer several advantages over autologous MSCs for clinical use, such as being readily available without invasive preparation, the long-term safety of allogeneic cells should be proven with corroborative evidence generated in advance. The safety of allogeneic human MSCs has been well-documented by Klyushnenkova et al. [49]. The authors suggested that MSCs were nonimmunogenic because they did not express major histocompatibility class II proteins and actually showed an immunosuppressive function through the inhibition of lymphocyte proliferation. One study compared the safety and efficacy of transendocardial injection of allogeneic and autologous MSCs to treat ischemic cardiomyopathy with a 12-month follow-up period [50]. After conducting that phase I/II randomized trial with 30 patients, the authors concluded that allogeneic MSCs were as safe and effective as autologous MSCs. In the musculoskeletal field, one study reported that intra-articular injection of allogeneic human MSC following partial medial meniscectomy improved meniscus regeneration and knee pain relief for 24 months, without any clinically relevant safety issues [51].

In this study, a minor degree of elbow joint effusions was observed in two participants (16.7%) of group 2 as adverse reactions, although the symptom was neither serious nor clinically significant. This phenomenon could be explained by stem cell leakage from the tendon defect area, which could induce cells to flow into a dependent area such as the elbow joint space, resulting in synovial irritation. Similar adverse reactions were also reported following injection with intra-articular platelet-rich plasma [52] and platelets rich in growth factors [53], which spontaneously resolved without significant complications, as in this study. Loftus et al. also suggested that intra-articular extension can occur (8%) during injection with platelet-rich plasma or autologous blood for treating tendinopathy [54]. Because slight intra-articular irritations naturally arise during the injection of any biological agent around tendon defect areas, any kind of scaffold that could retain the agents to abide around the target area should be needed in MSC injection to avoid the adverse event. In addition, regional swellings at the injection site observed in the half of the participants might not be acute immunological rejection to ASCs because the local swellings were transient and not accompanied with changes in the ratio of CD4-positive to CD8-positive T cells. It is interesting that similar post-injection inflammatory reaction of 48–72-hour window has been reported in stem cell trials of other species [55], providing possible mechanisms as irritation by fibrin itself [56] or serum-supplement for cell culture [57], hypersensitivity to fibrin sealant [58], or intratendinous injection per se [57]. Considering that the culturing process, as was used in preparation of our stem cells, can also provoke alteration of cell surface epitopes [59], it could be another possible mechanism of the post-injection inflammatory reaction. In addition, fetal bovine serum, which was used as serum-supplement for cell culture in this study, could have caused the inflammatory response [60]. Although subjects with known allergic or hypersensitive reaction to bovine-derived proteins of fibrin glue were excluded in this trial, screening by history would not have been thorough enough. Specific tests such as IgE antibody assays to bovine serum albumin [61] should be considered in future trials.

Efficacy of MSCs in Treating Tendinopathy

MSC applications in treating tendinopathy have been investigated in experimental animal models [26–29], with several studies providing encouraging results at the mechanical, histological, and molecular levels [62]. One study reported that MSCs could be induced to differentiate into tenocytes by overexpression of a bone morphogenetic protein 12 gene [63]. Only one previous clinical trial has reported the efficacy of stem cells in treating tendinopathy, which demonstrated that conventional rotator cuff repair with subsequent injection of mononuclear autologous stem cells from bone marrow enhanced shoulder functions and tissue integrity in the affected tendons [64]. However, in that study, stem cell therapy was used as an adjuvant in combination with tendon fixation by trans-osseous stitches. Therefore, the scarcity of clinical trials showing that human MSCs can form tendon-capable cells or tendons themselves makes it difficult to draw conclusions about clinical utility of these stem cells [65].

Although a clinical trial (NCT01687777) of MSCs for studying rotator cuff tendon repair has been recruiting since 2010 and another trial (NCT02064062) for Achilles tendinopathy plans to begin recruitment soon, no reports of MSCs for treating human tendinopathy have been published to date. While this was a pilot study with small set of participants, we did observe potential long-term improvements in pain, performance, and even structural defects in the lateral elbow tendon. In particular, elbow pain improved 78.7% throughout the study period; from an average VAS score of 66.8 mm at baseline to 14.8 mm at the 52-week follow-up visit.

The level of pain reduction observed in this study is better than those of previous clinical trials involving various therapeutic measures for LE, such as a 26.9% pain reduction following progressive strengthening exercises with heat therapy [66], a 63.1% reduction by myofascial release [67], a 62.3% reduction by conventional care with transcutaneous electrical nerve stimulation [7], a 67.1% reduction by percutaneous radiofrequency [45], a 51.4% reduction by lidocaine with epinephrine injection [68], and a 57.8% reduction by autologous whole blood injection [5]. Similar to our study, a 71.5% reduction in pain was recently reported by Mishra et al. as the

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result of a double-blind, prospective randomized controlled trial involving platelet-rich plasma injections to 230 LE patients with at least a 3-month symptom duration [20]. However, in this study, LE patients were enrolled who had experienced LE symptoms for more than 6 months [39], being intractable to previous treatments and having little chance to recover spontaneously. Moreover, all our patients had clear ultrasonographic defects, indicating that patients of simple tendinopathy or tenosynovitis without definite tendon tears were excluded. This inclusion criterion supports the assumption that our patients would not have improved so quickly unless the *allo*-ASC treatment because it was reported that the larger an intrasubstance tear was, the harder was it to achieve spontaneous improvement [69]. Considering the close relationship between the tear size and severity or intractability, it is of special note that we observed improvements not only in pain-related and functional outcomes but also in structural healing detected by ultrasonography 52 weeks post-treatment.

The efficacy of *allo*-ASC over other treatment options can be explained by the regenerative potential of MSCs. Three mechanisms for MSC-based therapy have been proposed [70]. First, MSCs can differentiate into the targeted cell type and contribute to wound repair [71]. Second, MSCs can secrete various cytokines and growth factors to adjacent cells (a paracrine effect), which may promote cellular proliferation in damaged tissues [72]. Third, MSCs have immunomodulatory properties that can reduce inflammation in injured tissues [73]. Interestingly, in this study, there was an apparent time-delay between the observation of clinical improvement and structural healing observed by ultrasonography. At least 26 weeks were required to detect significant structural healing in both the longitudinal and transverse views, while improvements of pain and performance were observed after only 6 weeks. The timing of these findings supports the third potential mechanism of MSC-induced regeneration, whereby the anti-inflammatory effects by MSC may occur prior to regeneration at the cellular or structural levels.

In this study, we assessed the dose-dependent response to *allo*-ASCs to treat LE by including groups that received either 10^6 cells (group 1) or 10^7 cells (group 2). While there were no significant differences in the changes of elbow pain and performance between the two groups at any of the follow-up visits, faster pain improvement and earlier plateauing of performance scores were observed in group 2. Although the number of participants was too small to conclude that the dose-dependent response of *allo*-ASC was significant, the higher concentration of stem cells tended to induce earlier clinical improvement. These potential dose-dependent relationships also support the efficacy of MSCs in treating tendinopathy. However, this study was a pilot study with a small sample size and no control group. Even though the patients were selected based on chronicity of symptoms, assuming that their condition would presumably not have improved as quickly as with allo-ASCs treatment, it is uncertain how much the lesions had already improved by the time of treatment and how much these lesions and clinical symptoms might have responded to a placebo treatment such as normal saline. Because we do not know the natural course of 12 participants, controlled studies should be needed to establish the definite efficacy of allo-ASCs. Therefore, it requires a discreet consideration to relate the positive results of this study with the potential effects of *allo*-ASC treatment. Further research with well-designed and larger randomized controlled trials appears necessary.

Another limitation of this study was that we could not distinguish whether defect-filling tissues observed by ultrasonography were collagen fibers from differentiated *allo*-ASC of the donors or proliferated damaged tendon tissues of the recipients. One experimental study involving xenotransplantation of human MSCs to the injured Achilles tendons of rats reported that the human MSCs survived and that these cells secreted human-specific collagen fibers [74]. However, further studies are needed to understand the precise mechanism of *allo*-ASCs in treating tendinopathy.

Quantitative Measurements of Tendon Defects by Ultrasonography

Ultrasonography has been one of the most commonly used imaging techniques to assess structural changes after injection treatments for tendinopathy [75] because of its capability to visualize soft tissue lesions at a relatively low cost, making it suitable for monitoring tendon lesions as frequently as is done in most clinical trials. Several ultrasonographic studies have been designed to measure pathological findings with the common extensor tendon using different quantitative methods. Jaen-Diaz et al. quantified tendon thickness, which correlated with a history of epicondylalgia [76]. Grading color Doppler activity from 0 to 4 has been used as a semiquantitative assessment of the severity of tendinopathy [75, 77]. Connell et al. adopted both semiquantitative and quantitative methods to grade hypoechogenicity and hypervascularity by measuring tendon thickness and tear sizes [30].

However, the authors speculated that these methods might not be appropriate to monitor changes of three-dimensional intratendinous defects, which is one of the fundamental outcomes after regenerative therapy. To overcome the limitations of conventional ultrasonographic measurements, we devised a novel quantitative method to measure the area of tendon defects in two orthogonal ultrasonographic views. Two blinded ultrasonographic examiners measured the area of the largest lesion of the CEO. Each examiner performed three repeat measurements in different random orders yielding intrarater reliabilities of 0.970 and 0.899, respectively, and an inter-rater reliability of 0.848. Although this method does not also provide three-dimensional volumetric measurements, the largest areas measured in two orthogonal views might give sufficient information regarding the total defect volume of tendon.

Conclusions

This pilot study on the safety and efficacy of *allo*-MSC injection for treating chronic LE demonstrated that the intervention was safe and efficacious in improving pain, performance, and anatomical defects for more than a 52-week follow-up period. This is the first clinical study using allogeneic MSCs to treat chronic tendinopathy.

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Author Contributions

S.G.C.: conception and design, clinical approach, manuscript writing, and final approval of manuscript; S.Y.L.: clinical approach, manuscript writing, and data analysis and interpretation; W.K.: conception and design and clinical approach; C.L.: clinical approach and collection of data.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

References

1 Kraushaar BS, Nirschl RP. Tendinosis of the elbow (tennis elbow). Clinical features and findings of histological, immunohistochemical, and electron microscopy studies. J Bone Joint Surg Am 1999;81:259–278.

2 Hong QN, Durand MJ, Loisel P. Treatment of lateral epicondylitis: Where is the evidence? Joint Bone Spine 2004;71:369–373.

3 Smidt N, van der Windt DA, Assendelft WJ et al. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: A randomised controlled trial. Lancet 2002;359:657–662.

4 Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: A systematic review of randomised controlled trials. Lancet 2010;376:1751–1767.

5 Thanasas C, Papadimitriou G, Charalambidis C et al. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: A randomized controlled clinical trial. Am J Sports Med 2011;39:2130–2134.

6 Bisset L, Beller E, Jull G et al. Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: Randomised trial. BMJ 2006;333:939.

7 Chesterton LS, Lewis AM, Sim J et al. Transcutaneous electrical nerve stimulation as adjunct to primary care management for tennis elbow: Pragmatic randomised controlled trial (TATE trial). BMJ 2013;347:f5160.

8 Faes M, van den Akker B, de Lint JA et al. Dynamic extensor brace for lateral epicondylitis. Clin Orthop Relat Res 2006;442:149–157.

9 Tyler TF, Thomas GC, Nicholas SJ et al. Addition of isolated wrist extensor eccentric exercise to standard treatment for chronic lateral epicondylosis: A prospective randomized trial. J Shoulder Elbow Surg 2010;19:917–922.

10 Cho BK, Kim YM, Kim DS et al. Mini-open muscle resection procedure under local anesthesia for lateral and medial epicondylitis. Clin Orthop Surg 2009;1:123–127.

11 Wong MW, Tang YN, Fu SC et al. Triamcinolone suppresses human tenocyte cellular activity and collagen synthesis. Clin Orthop Relat Res 2004:277–281.

12 Fredberg U. Local corticosteroid injection in sport: Review of literature and guidelines for treatment. Scand J Med Sci Sports 1997;7:131–139.

13 Sweetnam R. Corticosteroid arthropathy and tendon rupture. J Bone Joint Surg Br 1969;51:397–398.

14 Rabago D, Lee KS, Ryan M et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): Results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil 2013;92:587–596.

15 Scarpone M, Rabago DP, Zgierska A et al. The efficacy of prolotherapy for lateral epicondylosis: A pilot study. Clin J Sport Med 2008;18:248–254.

16 Connell DA, Ali KE, Ahmad M et al. Ultrasound-guided autologous blood injection for tennis elbow. Skeletal Radiol 2006;35:371–377.

17 Gosens T, Peerbooms JC, van Laar W et al. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: A double-blind randomized controlled trial with 2-year follow-up. Am J Sports Med 2011;39:1200–1208.

18 Foster TE, Puskas BL, Mandelbaum BR et al. Platelet-rich plasma: From basic science to clinical applications. Am J Sports Med 2009;37:2259–2272.

19 de Mos M, van der Windt AE, Jahr H et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. Am J Sports Med 2008;36:1171–1178.

20 Mishra AK, Skrepnik NV, Edwards SG et al. Efficacy of platelet-rich plasma for chronic tennis elbow: A double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med 2014;42:463–471.

21 Raeissadat SA, Sedighipour L, Rayegani SM et al. Effect of platelet-rich plasma (PRP) versus autologous whole blood on pain and function improvement in tennis elbow: A randomized clinical trial. Pain Res Treat 2014;2014:191525.

22 Rabago D, Best TM, Zgierska AE et al. A systematic review of four injection therapies for lateral epicondylosis: Prolotherapy, polidocanol, whole blood and platelet-rich plasma. Br J Sports Med 2009;43:471–481.

23 de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: A systematic review. Br J Sports Med 2014;48:952–956.

24 Reed SA, Leahy ER. Growth and development symposium: Stem cell therapy in equine tendon injury. J Anim Sci 2013;91:59–65.

25 Godwin EE, Young NJ, Dudhia J et al. Implantation of bone marrow-derived mesenchymal stem cells demonstrates improved outcome in horses with overstrain injury of the superficial digital flexor tendon. Equine Vet J 2012;44:25–32.

26 Yao J, Woon CY, Behn A et al. The effect of suture coated with mesenchymal stem cells and bioactive substrate on tendon repair strength in a rat model. J Hand Surg Am 2012;37:1639–1645.

27 Okamoto N, Kushida T, Oe K et al. Treating Achilles tendon rupture in rats with bone-marrow-cell transplantation therapy. J Bone Joint Surg Am 2010;92:2776–2784.

28 Chong AK, Ang AD, Goh JC et al. Bone marrow-derived mesenchymal stem cells influence early tendon-healing in a rabbit achilles tendon model. J Bone Joint Surg Am 2007;89:74–81.

29 Uysal CA, Tobita M, Hyakusoku H et al. Adipose-derived stem cells enhance primary tendon repair: Biomechanical and immunohistochemical evaluation. J Plast Reconstr Aesthet Surg 2012;65:1712–1719.

30 Connell D, Datir A, Alyas F et al. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. Br J Sports Med 2009;43:293–298.

31 Clarke AW, Alyas F, Morris T et al. Skin-derived tenocyte-like cells for the treatment of patellar tendinopathy. Am J Sports Med 2011;39:614–623.

32 Lee WY, Park KJ, Cho YB et al. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. Stem Cells 2013;31:2575–2581.

33 de Girolamo L, Lucarelli E, Alessandri G et al. Mesenchymal stem/stromal cells: A new "cells as drugs" paradigm. Efficacy and critical aspects in cell therapy. Curr Pharm Des 2013;19:2459–2473.

34 Lalu MM, McIntyre L, Pugliese C et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): A systematic review and meta-analysis of clinical trials. PLoS One 2012;7:e47559.

35 Holtick U, Albrecht M, Chemnitz JM et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. Cochrane Database Syst Rev 2014;4:CD010189.

36 Pidala J, Djulbegovic B, Anasetti C et al. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. Cochrane Database Syst Rev 2011:CD008818.

37 Ricco S, Renzi S, Del Bue M et al. Allogeneic adipose tissue-derived mesenchymal stem cells in combination with platelet rich plasma are safe and effective in the therapy of superficial digital flexor tendonitis in the horse. Int J Immunopathol Pharmacol 2013;26(suppl 1):61–68.

38 de la Portilla F, Alba F, Garcia-Olmo D et al. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: Results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis 2013;28:313–323.

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39 Wang A, Breidahl W, Mackie KE et al. Autologous tenocyte injection for the treatment of severe, chronic resistant lateral epicondylitis: A pilot study. Am J Sports Med 2013;41:2925–2932.
40 Ivy SP, Siu LL, Garrett-Mayer E et al. Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: A report from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clin Cancer Res 2010;16:1726–1736.
41 Franklin HR, Simonetti GP, Dubbelman AC et al. Toxicity grading systems. A comparison between the WHO scoring system and the Common Toxicity Criteria when used for nausea and vomiting. Ann Oncol 1994;5:113–117.
42 Evans CH, Robbins PD, Ghivizzani SC et al. Clinical trial to assess the safety, feasibility, and efficacy of transferring a potentially anti-arthritic cytokine gene to human joints with rheumatoid arthritis. Hum Gene Ther 1996;7:1261–1280.
43 Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am J Sports Med 2006; 34:1774–1778.
44 Turchin DC, Beaton DE, Richards RR. Validity of observer-based aggregate scoring systems as descriptors of elbow pain, function, and disability. J Bone Joint Surg Am 1998;80:154–162.
45 Lin CL, Lee JS, Su WR et al. Clinical and ultrasonographic results of ultrasonographically guided percutaneous radiofrequency lesioning in the treatment of recalcitrant lateral epicondylitis. Am J Sports Med 2011;39: 2429–2435.
46 Rubio D, Garcia-Castro J, Martin MC et al. Spontaneous human adult stem cell transformation. Cancer Res 2005;65:3035–3039.
47 de la Fuente R, Bernad A, Garcia-Castro J et al. Retraction: Spontaneous human adult stem cell transformation. Cancer Res 2010; 70:6682.
48 Klopp AH, Gupta A, Spaeth E et al. Concise review: Dissecting a discrepancy in the literature: Do mesenchymal stem cells support or suppress tumor growth? Stem Cells 2011;29:11–19.
49 Klyushnenkova E, Mosca JD, Zernetkina V et al. T cell responses to allogeneic human mesenchymal stem cells: Immunogenicity, tolerance, and suppression. J Biomed Sci 2005;12:47–57.
50 Hare JM, Fishman JE, Gerstenblith G et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: The POSEIDON randomized trial. JAMA 2012; 308:2369–2379.
51 Vangsness CT, Jr., Farr J, 2nd, Boyd J et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: A randomized, double-blind, controlled study. J Bone Joint Surg Am 2014;96:90–98.
52 Filardo G, Kon E, Di Martino A et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. BMC musculoskelet Disord 2012; 13:229.
53 Sanchez M, Anitua E, Azofra J et al. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: A retrospective cohort study. Clin Exp Rheumatol 2008;26:910–913.
54 Loftus ML, Endo Y, Adler RS. Retrospective analysis of postinjection ultrasound imaging after platelet-rich plasma or autologous blood: Observational review of anatomic distribution of injected material. AJR Am J Roentgenol 2012;199:W501–505.
55 Carrade DD, Owens SD, Galuppo LD et al. Clinicopathologic findings following intra-articular injection of autologous and allogeneic placentally derived equine mesenchymal stem cells in horses. Cytotherapy 2011;13:419–430.
56 Cakmak O, Babakurban ST, Akkuzu HG et al. Injectable tissue-engineered cartilage using commercially available fibrin glue. Laryngoscope 2013;123:2986–2992.
57 Renzi S, Ricco S, Dotti S et al. Autologous bone marrow mesenchymal stromal cells for regeneration of injured equine ligaments and tendons: A clinical report. Res Vet Sci 2013;95:272–277.
58 Beierlein W, Scheule AM, Antoniadis G et al. An immediate, allergic skin reaction to aprotinin after reexposure to fibrin sealant. Transfusion 2000;40:302–305.
59 Peister A, Mellad JA, Larson BL et al. Adult stem cells from bone marrow (MSCs) isolated from different strains of inbred mice vary in surface epitopes, rates of proliferation, and differentiation potential. Blood 2004;103:1662–1668.
60 Macy E, Bulpitt K, Champlin RE et al. Anaphylaxis to infusion of autologous bone marrow: An apparent reaction to self, mediated by IgE antibody to bovine serum albumin. J Allergy Clin Immunol 1989;83:871–875.
61 Mackensen A, Drager R, Schlesier M et al. Presence of IgE antibodies to bovine serum albumin in a patient developing anaphylaxis after vaccination with human peptide-pulsed dendritic cells. Cancer Immunol Immunother 2000;49:152–156.
62 Ahmad Z, Wardale J, Brooks R et al. Exploring the application of stem cells in tendon repair and regeneration. Arthroscopy 2012;28:1018–1029.
63 Wang QW, Chen ZL, Piao YJ. Mesenchymal stem cells differentiate into tenocytes by bone morphogenetic protein (BMP) 12 gene transfer. J Biosci Bioeng 2005;100:418–422.
64 Ellera Gomes JL, da Silva RC, Silla LM et al. Conventional rotator cuff repair complemented by the aid of mononuclear autologous stem cells. Knee Surg Sports Traumatol Arthrosc 2012;20:373–377.
65 Bullough R, Finnigan T, Kay A et al. Tendon repair through stem cell intervention: Cellular and molecular approaches. Disabil Rehabil 2008;30:1746–1751.
66 Oken O, Kahraman Y, Ayhan F et al. The short-term efficacy of laser, brace, and ultrasound treatment in lateral epicondylitis: A prospective, randomized, controlled trial. J Hand Ther 2008;21:63–67.
67 Ajimsha MS, Chithra S, Thulasyammal RP. Effectiveness of myofascial release in the management of lateral epicondylitis in computer professionals. Arch Phys Med Rehabil 2012;93:604–609.
68 Zeisig E, Fahlstrom M, Ohberg L et al. Pain relief after intratendinous injections in patients with tennis elbow: Results of a randomised study. Br J Sports Med 2008;42:267–271.
69 Clarke AW, Ahmad M, Curtis M et al. Lateral elbow tendinopathy: Correlation of ultrasound findings with pain and functional disability. Am J Sports Med 2010;38:1209–1214.
70 Wang J, Liao L, Tan J. Mesenchymal-stem-cell-based experimental and clinical trials: Current status and open questions. Expert Opin Biol Ther 2011;11:893–909.
71 Sasaki M, Abe R, Fujita Y et al. Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type. J Immunol 2008;180:2581–2587.
72 Chen L, Tredget EE, Wu PY et al. Paracrine factors of mesenchymal stem cells recruit macrophages and endothelial lineage cells and enhance wound healing. PLoS One 2008;3:e1886.
73 Rasmusson I, Ringden O, Sundberg B et al. Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms. Exp Cell Res 2005;305:33–41.
74 Machova Urdzikova L, Sedlacek R, Suchy T et al. Human multipotent mesenchymal stem cells improve healing after collagenase tendon injury in the rat. Biomed Eng Online 2014;13:42.
75 Krogh TP, Fredberg U, Stengaard-Pedersen K et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: A randomized, double-blind, placebo-controlled trial. Am J Sports Med 2013;41:625–635.
76 Jaen-Diaz JI, Cerezo-Lopez E, Lopez-de Castro F et al. Sonographic findings for the common extensor tendon of the elbow in the general population. J Ultrasound Med 2010;29:1717–1724.
77 Poltawski L, Ali S, Jayaram V et al. Reliability of sonographic assessment of tendinopathy in tennis elbow. Skeletal Radiol 2012; 41:83–89..


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