Intratendinous Injection of Mesenchymal Stem Cells for the Treatment of Rotator Cuff Disease: A 2-Year Follow-Up Study

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Purpose: To assess the mid-term safety and efficacy of an intratendinous injection of autologous adipose tissue–derived mesenchymal stem cells (AD MSCs) for rotator cuff disease at 2-year follow-up. **Methods:** The first part of the study consisted of 3 dose-escalation groups, with 3 patients each, for the evaluation of safety: low-dose (1.0×10^7 cells), mid-dose (5.0×10^7), and high-dose (1.0×10^8) groups. For the second part, we planned to include 9 patients receiving the high dose for the evaluation of exploratory efficacy. Clinical outcomes were assessed according to pain, range of motion, muscle strength, functional scores, overall satisfaction and function, and presence of failure. Structural outcomes included changes in volume of tendon defects measured using magnetic resonance imaging. **Results:** This study enrolled 19 patients (9 for the first part and 10 for the second part) with partial-thickness rotator cuff tears. There were no treatment-related adverse events at minimum 2-year follow-up. Intratendinous injection of AD MSCs reduced shoulder pain by approximately 90% at 1 and 2 years in the mid- and high-dose groups. The strength of the supraspinatus, infraspinatus, and teres minor significantly increased by greater than 50% at 2 years in the high-dose group. Shoulder function measured with 6 commonly used scores improved for up to 2 years in all dose groups. Structural outcomes evaluated with magnetic resonance imaging showed that the volume of bursal-sided defects in the high-dose group nearly disappeared at 1 year and did not recur at up to 2 years. No failures—defined as the performance of any kind of shoulder surgery or return of the Shoulder Pain and Disability Index score to the preinjection level—occurred during follow-up. **Conclusions:** This study showed continued safety and efficacy of an intratendinous injection of AD MSCs for the treatment of partial-thickness rotator cuff tears over a 2-year period through regeneration of tendon defects. **Level of Evidence:** Level III, retrospective comparative study.

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Shoulder pain is a common musculoskeletal disease with a lifetime prevalence of 6.7% to 66.6% next to those of back pain and knee pain.[1] It is most common in patients in their forties and fifties, the ages of highest productivity, posing a substantial socioeconomic burden.[2] Rotator cuff disease is one of the most common causes of shoulder pain and can be defined as chronic progressive degenerative disease of the rotator cuff tendon.[3-5] A variety of treatment options can be applied in patients depending on age, demand, symptoms, stage of disease, and physical examination and imaging findings, ranging from conservative treatment

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such as activity modification, physical therapy and exercise, nonsteroidal anti-inflammatory drugs, and various injections to surgery including acromioplasty, rotator cuff repair, and arthroplasty.[6] Despite favorable results, none of these treatments can halt or reverse the progression of disease through regeneration of the rotator cuff, suggesting the necessity for new treatment alternatives. Recent advances in cell therapy with mesenchymal stem cells (MSCs) show potential in the treatment of rotator cuff disease.[7-10]

The delivery of MSCs for tendon regeneration has mostly been performed via surgical implantation with or without a scaffold in acute transection or window defects in animal models. However, a degenerative tendon defect in rotator cuff disease is generally an unconfined lesion with poorly defined boundaries of the frayed tendon end. Furthermore, surgical debridement of degenerated tissues to the grossly intact portion of tendon does not necessarily provide optimal healing potential because tendon degeneration may exist throughout the tendon.[11,12] Some in vivo studies performed intratendinous injections of MSCs and showed promising results.[13,14] Although the exact mechanism is not known, application of MSCs via injection could provide a meaningful treatment opportunity to many patients.

In 2018, we reported a first-in-human trial of intratendinous injection of autologous adipose tissue–derived (AD) MSCs for the treatment of rotator cuff disease.[10] The study showed the safety and efficacy of an intratendinous injection of AD MSCs with clinical, radiologic, and arthroscopic evidence at 6 months' follow-up, but no mid-term results were reported. Thus, the purpose of this follow-up study was to assess the safety and efficacy of an intratendinous injection of autologous AD MSCs in patients with rotator cuff disease at a minimum follow-up of 2 years. We hypothesized that intratendinous injection of AD MSCs would reduce pain and improve shoulder function through regeneration of the rotator cuff tendon.

Methods

Patient Data and Follow-Up

This was a retrospective study with prospectively collected data from a previous prospective study conducted between July 2015 and November 2016 as an open-label, single-center, dose-escalation trial of an intratendinous injection of autologous AD MSCs for the treatment of patients with partial-thickness rotator cuff tears (ClinicalTrials.gov identifier NCT02474342) The first part of the study consisted of 3 dose-escalation cohorts, with 3 patients in each cohort, for the evaluation of safety and tolerability: low dose (1.0×10^7 cells), mid dose (5.0×10^7 cells), and high dose (1.0×10^8 cells). For the second part, we planned to include 9 patients receiving the high dose for the evaluation of exploratory efficacy. Eligible patients were aged 19 years or older; had a duration of symptoms, consisting of unilateral shoulder pain, for more than 3 months; and had a partial-thickness rotator cuff tear identified with ultrasonography or magnetic resonance imaging (MRI). Details of the dose-escalation method and inclusion and exclusion criteria are presented in Appendixes 1 and 2 (available at www.arthroscopyjournal.org).

All pain medications except the rescue analgesic were discontinued during the trial. Patients were followed up at 1 month, 3 months, 6 months, 1 year, and 2 years after injection. At each visit, safety and efficacy assessments were performed. MRI of the shoulder was also obtained at 1 month, 3 months, 6 months, 1 year, and 2 years after injection. Second-look arthroscopy was performed at 6 months after injection. The study was approved by the institutional review board of our institute. Independent safety and data monitors oversaw the overall trial process.

Preparation and Injection of AD MSCs

AD MSCs were isolated from abdominal subcutaneous fat by liposuction and cultured under current good manufacturing practice conditions for approximately 3 weeks as previously described.[10] MSCs were tested for cell number, viability, purity (CD31, CD34, and CD45), identity (CD73 and CD90), sterility, endotoxin, and mycoplasma before being shipped.

After an arthroscopic examination of the glenohumeral joint and subacromial space, AD MSCs in 3 mL of saline solution were injected into the anterior, center, and posterior one-third of the torn end of the rotator cuff through the lateral aspect of the shoulder under ultrasonographic guidance using a 22-gauge spinal needle. No synovectomy or debridement of any tissues was performed during arthroscopy, and no drain was used.

Shrugging, protraction, and retraction of the shoulder girdle; intermittent elbow, wrist, and hand exercise; and external rotation of the arm to neutral with a brace were encouraged as tolerated, usually immediately after injection. Further passive and active-assisted range of motion (ROM) exercises were allowed after patients were gradually weaned off the abduction brace starting at 4 weeks after injection. Patients began strengthening exercises as soon as ROM was recovered.

Clinical and Structural Outcomes

Safety was assessed based on adverse events. Adverse events were categorized using the National Cancer Institute Common Terminology Criteria for Adverse Events scale, version 4.0. Clinical outcomes were assessed according to (1) pain, (2) ROM, (3) muscle

strength, (4) six commonly used functional scores, (5) overall satisfaction and function, and (6) presence of failure. A visual analog scale (VAS) was used to evaluate pain at rest, with motion, and at night; patients rated their pain on a 10-cm scale ranging from "no pain" to "unbearable pain." Mean pain scores and scores of patients' worst pain were also recorded. ROM was assessed as previously described.[15] The strength of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles was measured with a handheld electronic scale (CHS; CAS, Gyeonggi-do, Korea). The strength of the infraspinatus was measured as strength in external rotation with the arm at the side, and that of the teres minor was measured with the arm in 90° of abduction. The functional scoring systems included the Shoulder Pain and Disability Index (SPADI) score; Constant score; American Shoulder and Elbow Surgeons score; University of California, Los Angeles score; Simple Shoulder Test score; and Disabilities of the Arm, Shoulder and Hand score. Using a 10-cm scale, we evaluated overall function and satisfaction, with patients marking their responses from "I cannot use it" to "I feel normal" for overall function (Single Assessment Numeric Evaluation) and from "never satisfied" to "very satisfied" for overall satisfaction. Failure of AD MSC injection was defined as either the performance of any kind of surgery, including shoulder arthroscopy and arthroplasty, because of rotator cuff disease or the return of the original primary functional outcome (SPADI score) to its baseline value or lower at more than 6 months after injection. Structural outcomes included changes in volume of tendon defects in the supraspinatus and infraspinatus measured using MRI between the time of cell injection and evaluation at 6, 12, and 24 months after injection by a blinded musculoskeletal radiologist (J.W.C.), as previously described (Appendix 3, available at www.arthroscopyjournal.org).

Statistical Analyses

Analysis was performed according to the cell dose levels (low-, mid-, and high-dose levels) and according to the intention-to-treat principle for clinical and structural outcomes. All primary analyses were performed based on the intention-to-treat principle. For analyses of outcome measures, missing data were replaced with the multiple imputation—by—chained equation method under a missing-at-random assumption. Ten imputed data sets were generated and analyzed separately in each imputed data set for each outcome measure. The results were then combined across imputations using the method of Rubin.[16] In addition, a complete case analysis and the last observation—carried forward method were conducted for a sensitivity analysis. Because all 3 methods showed similar results, we presented only the imputation analyses. A paired t test was used to assess the within-group change from baseline at each follow-up time point. The level of statistical significance was set at $P < .05$. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC) and the R program (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

Follow-Up of Patients

Twenty patients were consecutively allocated to the treatment groups; 1 patient withdrew his consent after liposuction, and thus, 19 patients (9 for the first part of the study and 10 for the second part) received AD MSCs (Fig 1). The baseline characteristics of the patients were not significantly different among the treatment groups except for the SPADI score (Table 1). There were 14 female and 5 male patients, with a mean age of 57.1 ± 9.6 years (range, 35-76 years). Patients had shoulder pain for at least 7 months, without a history of shoulder surgery. MRI examination before injection identified 4 articular-sided tears (21%), 14 bursal-sided tears (74%), and 3 intratendinous tears (16%). One patient was excluded because he was found to have a focal full-thickness tear just after cell injection; he was later treated with arthroscopic rotator cuff repair. Of the 18 patients who participated in the previous study, 17 were followed up at 1 and 2 years. One patient in the mid-dose group was not available for follow-up at 1 and 2 years. None of the patients underwent any kind of shoulder surgery including arthroscopy and arthroplasty during the 2-year period after surgery.

Clinical Outcomes

No clinically important or treatment-related adverse event occurred during the follow-up period of 2 years (Appendix 4, available at www.arthroscopyjournal.org). All of the VAS scores for pain significantly decreased at 1 and 2 years after injection in all dose groups except for pain at rest and night pain in the low-dose group (Fig 2; Appendix 5, available at www.arthroscopyjournal.org).

VAS scores for pain with motion in the low-, mid-, and high-dose groups decreased by 84.4%, 92.2%, and 82.2%, respectively, at 1 year compared with those at baseline. At 2 years, they further decreased by 89.6%, 94.4%, and 92.2%, respectively. External rotation in the mid-dose group, external rotation in the high-dose group, and internal rotation in the high-dose group significantly increased by 53.5%, 27.7%, and 16.4%, respectively, at 2 years (Appendix 6, available at www.arthroscopyjournal.org). No significant improvement was observed in the other ROM values. The strength of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles decreased because of

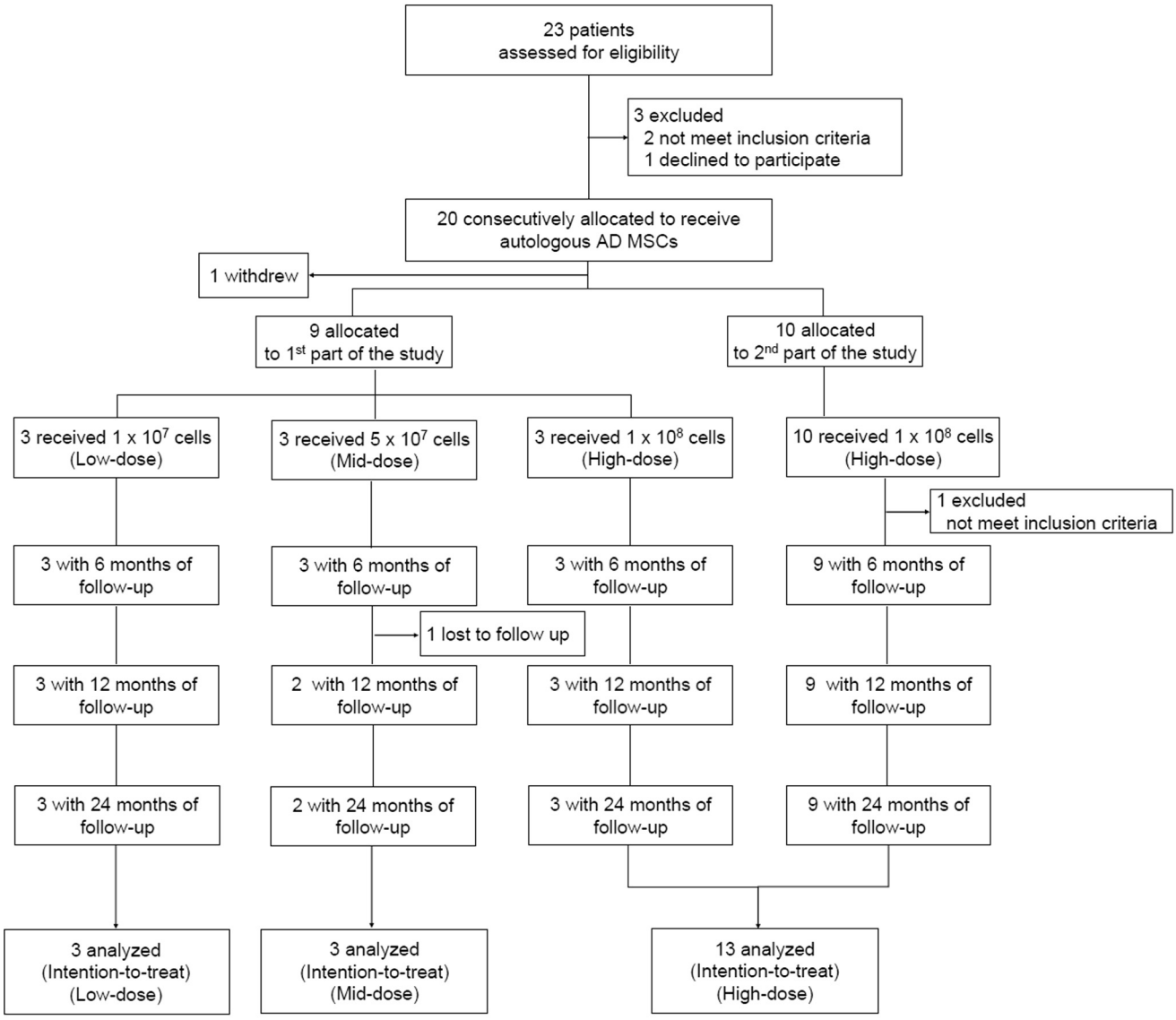

Figure 1. Study flow diagram. (AD MSCs, adipose tissue–derived mesenchymal stem cells; F/U, follow-up; M, months; MRI, magnetic resonance imaging; W, weeks.)

Table 1. Baseline Characteristics of Patients

Variable	Low (1×10^7 Cells Injected)	Mid (5×10^7 Cells Injected)	High (1×10^8 Cells Injected)
Patients, n	3	3	13
Age, yr	65.7 ± 9.1	50.3 ± 13.4	56.9 ± 9.7
Sex			
Male	1 (33)	2 (67)	2 (15)
Female	2 (67)	1 (33)	11 (85)
Height, cm	158.7 ± 15.1	160.7 ± 13.5	155.9 ± 5.6
Weight, kg	60.5 ± 19.7	65.0 ± 13.3	58.0 ± 9.4
Body mass index	23.5 ± 3.3	25.0 ± 1.1	23.7 ± 2.6
Dominance			
Yes	2 (67)	3 (100)	13 (100)
No	1 (33)	0	0
Symptom duration, mo	23.0 ± 15.5	7.4 ± 4.4	28.8 ± 25.3
Treatment history*			
Surgery	0	0	0
Pharmaceutical treatment	3 (100)	3 (100)	13 (100)
Injection	1 (33)	2 (67)	10 (77)
Physiotherapy	1 (33)	2 (67)	7 (54)
Acupuncture	1 (33)	0	4 (31)
VAS score for pain with motion	7.7 ± 15.3	9.0 ± 10.0	9.0 ± 5.8
SPADI score	44.1 ± 11.8	63.8 ± 8.5	75.4 ± 9.9
Constant score	60.8 ± 16.7	60.9 ± 11.0	55.7 ± 6.5
Tear location†			
Articular side	0	0	4 (31)
Bursal side	3 (100)	3 (100)	8 (62)
Intratendinous	1 (33)	0	2 (15)

NOTE. Data are presented as number (percentage) or mean ± standard deviation.

SPADI, Shoulder Pain and Disability Index; VAS, visual analog scale.

*Each patient was asked whether he or she received surgery, pharmaceutical treatment, injection, physiotherapy, or acupuncture during the past 3 months (yes or no).

†The tear location was identified with magnetic resonance imaging examination before injection.

immobilization early after injection and then reversed to increase upward up to 2 years (Fig 2; Appendix 6, available at www.arthroscopyjournal.org). In the low-dose group, the strength of the infraspinatus significantly increased by 20% at 2 years. In the high-dose group, the strength of the supraspinatus, infraspinatus, and teres minor significantly increased by 41.5%, 46.6%, and 39.1%, respectively, at 1 year and by 72.3%, 60.3%, and 55.1%, respectively, at 2 years.

The SPADI scores in the low-, mid-, and high-dose groups significantly decreased by 77.3%, 87.0%, and 80.8%, respectively, at 1 year compared with those at baseline (Fig 3; Appendix 7, available at www.arthroscopyjournal.org). At 2 years, they further decreased by 85.5%, 91.5%, and 90.2%, respectively. The Constant scores in the low-dose group increased up to 2 years without significance. Meanwhile, in the mid- and high-dose groups, they significantly increased by 32.2% and 32.9%, respectively, at 1 year and by 38.6% and 44.2%, respectively, at 2 years. The American Shoulder and Elbow Surgeons scores in the mid- and high-dose groups significantly increased by 104.6% and 162.2%, respectively, at 1 year. At 2 years, they increased by 50.1%, 105.5%, and 179.4% in the low-, mid-, and high-dose groups, respectively. The University of California, Los Angeles scores in the mid- and high-dose groups significantly increased by 74.9% and 98.0%, respectively, at 1 year and by 79.2% and 110.5%, respectively, at 2 years. The Simple Shoulder Test scores in the high-dose group significantly increased by 120.5% at 1 year and 145.5% at 2 years. The Disabilities of the Arm, Shoulder and Hand scores in the mid- and high-dose groups significantly decreased by 82.5% and 69.1%, respectively, at 1 year and by 87.0% and 83.5%, respectively, at 2 years. Overall function in the mid- and high-dose groups significantly increased by 143.3% (from 36.7 to 89.3) and by 113.5% (from 37.7 to 80.5), respectively, at 1 year (Appendix 8, available at www.arthroscopyjournal.org). It further improved by 155.3% (to 93.7) and by 134.8% (to 88.5), respectively, at 2 years. Overall satisfaction was over 93% at 2 years in all dose groups. No failure of AD MSC injection occurred during 2 years of follow-up.

Structural Outcomes

MRI assessment of tendon defects showed that the volume of bursal-sided defects in the high-dose group significantly decreased by 96.8% at 1 year and 100.0% at 2 years (Fig 4; Appendix 9, available at www.arthroscopyjournal.org). Meanwhile, nonsignificant

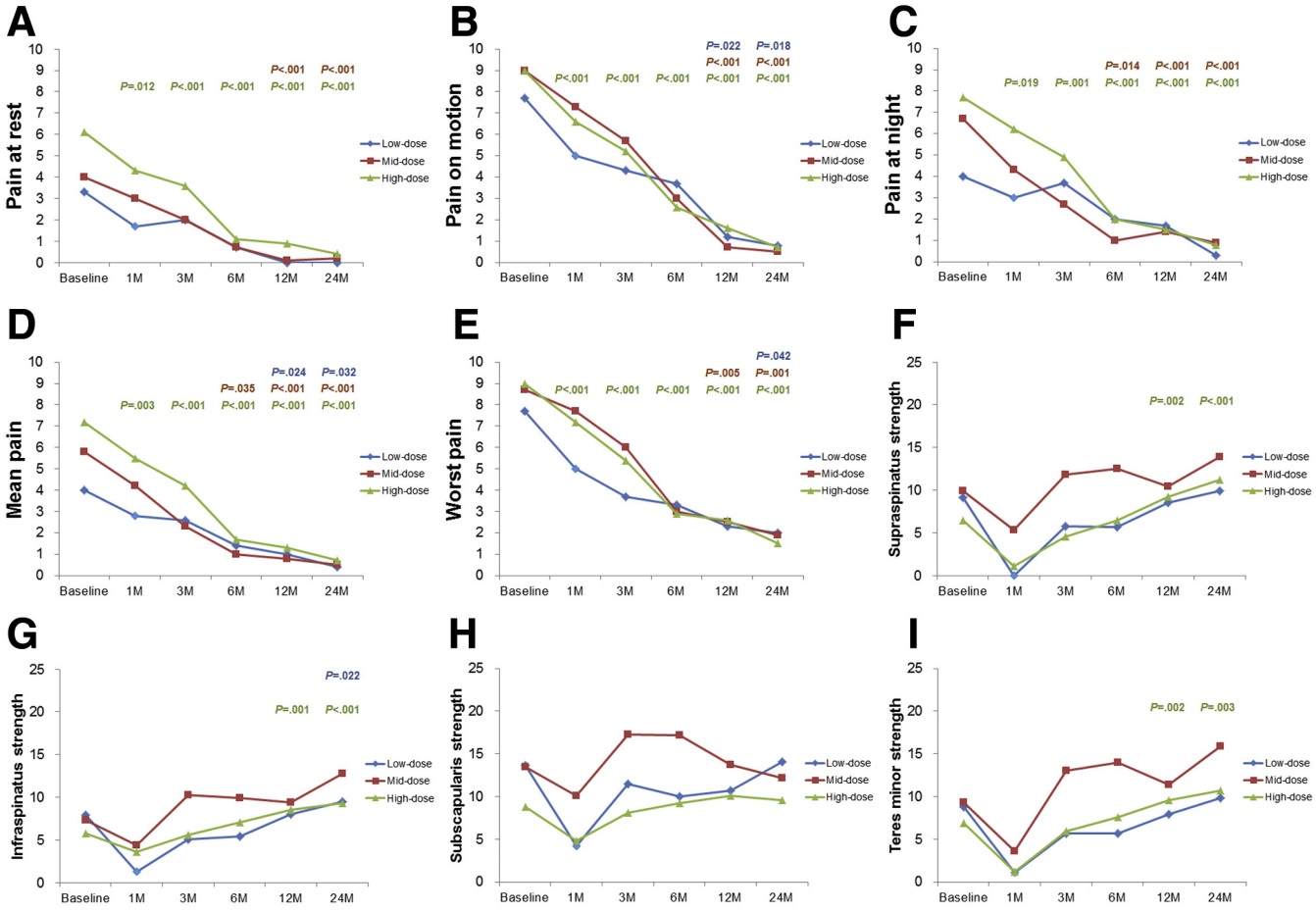

Figure 2. Changes in visual analog scale scores for pain at rest (A), with motion (B), and at night (C); mean pain score (D); worst pain score (E); and strength of supraspinatus (F), infraspinatus (G), subscapularis (H), and teres minor (I) after intratendinous injection of adipose tissue–derived mesenchymal stem cells. *P* values for improvement are described with respect to the dose groups. Data up to 6 months are reprinted with permission.[10] (M, months.)

decreases in the volume of articular-sided defects in the high-dose group, bursal-sided defects in the low- and mid-dose groups, and intratendinous defects in the low-dose group, as well as nonsignificant increases in the volume of intratendinous defects in the high-dose group, were identified.

Discussion

The most important findings of this follow-up study are as follows: (1) Intratendinous injection of autologous AD MSCs into torn rotator cuffs was not associated with apparent adverse events up to 2 years. (2) All pain scores measured in the study significantly decreased by approximately 90% at 1 and 2 years, with the exception of nonsignificant decreases in pain at rest and at night in the low-dose group. (3) The strength of the supraspinatus, infraspinatus, and teres minor significantly increased by greater than 50% at 2 years in the high-dose group. Nonsignificant increases were found in the low- and mid-dose groups. (4) Shoulder function measured with 6 commonly used scores improved for up to 2 years in all dose groups. However, statistical significance was found mainly in the high-dose group. (5) Structural outcomes evaluated with MRI showed that the volume of bursal-sided defects in the high-dose group nearly disappeared at 1 year and did not recur at up to 2 years. One noteworthy finding is that both clinical and structural outcomes seem to continue to improve through the 2-year follow-up. Taken together, the results with 2-year follow-up showed the safety and efficacy of an intratendinous injection of AD MSCs through regeneration of tendon defects for the treatment of rotator cuff disease. These results suggest that this could be a promising approach as a fundamental treatment strategy that would modify, halt, or possibly reverse the natural course of the disease.

Given that the natural healing potential of tendons is extremely low and inefficient probably because of hypocellularity and hypovascularity, rotator cuff disease progresses without spontaneous healing from tendinopathy to a partial-thickness tear, a full-thickness tear, and eventually, cuff tear arthropathy whether it is

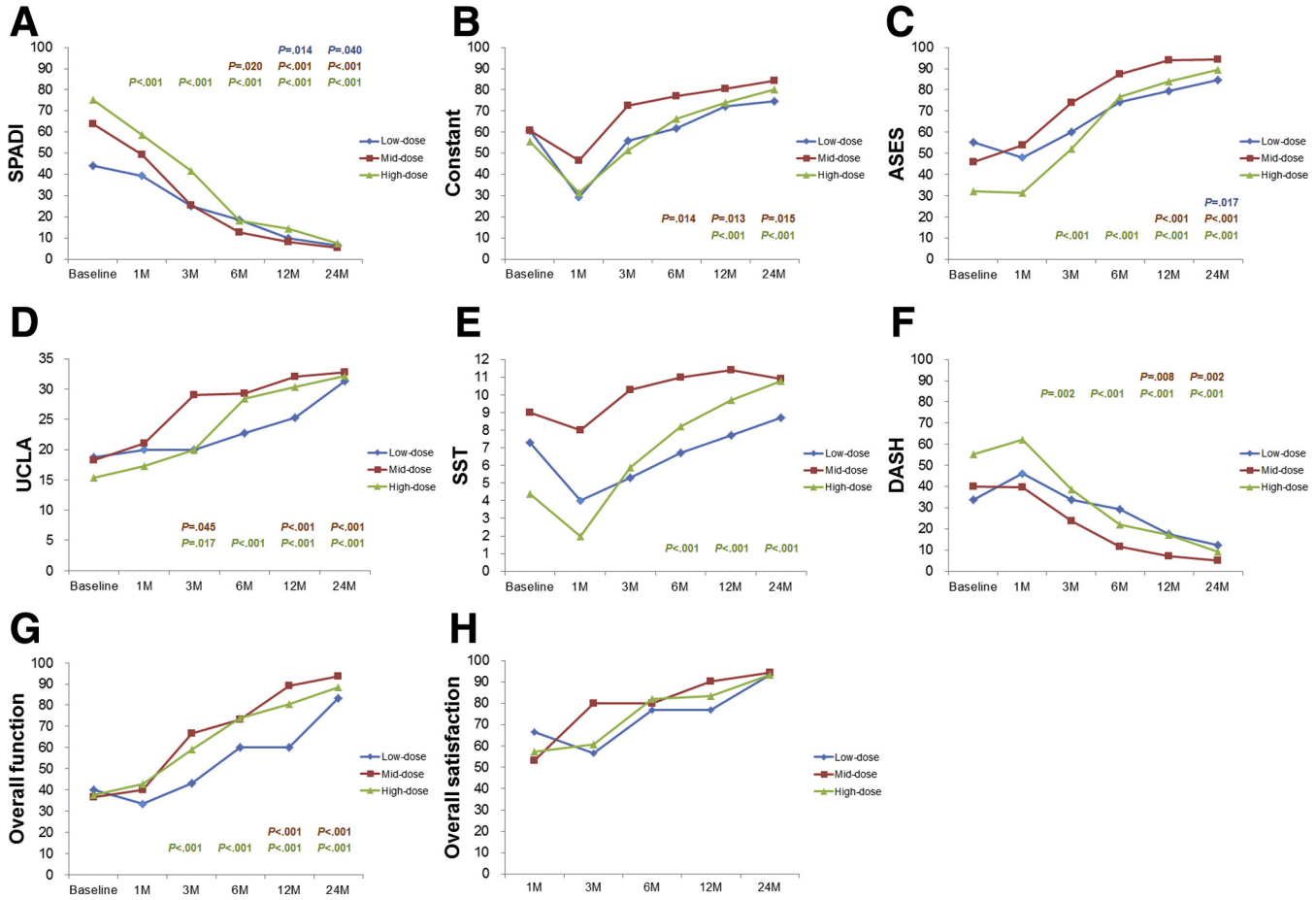

Figure 3. Changes in Shoulder Pain and Disability Index (SPADI) score (A); Constant score (B); American Shoulder and Elbow Surgeons (ASES) score (C); University of California, Los Angeles (UCLA) score (D); Simple Shoulder Test (SST) score (E); Disabilities of the Arm, Shoulder and Hand (DASH) score (F); overall function (G); and overall satisfaction (H) after intratendinous injection of adipose tissue–derived mesenchymal stem cells. *P* values for improvement are described with respect to the dose groups. Data up to 6 months are reprinted with permission.[10] (M, months.)

symptomatic or not.[3,17-19] Progression of rotator cuff disease does not only mean an increase in tendon defect size; it may also cause deterioration of tendon quality, degeneration of rotator cuff muscles, local osteoporosis of the proximal humerus, and osteoarthritis of the glenohumeral joint.[20-22] With respect to progression of a partial-thickness tear, several studies have consistently shown that healing is scarce but progression of the tear is common.[23,24] Yamanaka and Matsumoto[25] reported that partial-thickness cuff tears propagated in 53% of cases and became full-thickness tears in 28% but healed in 10% and became smaller in 10%. Recently, using MRI, Yamamoto et al.[26] reported that partial-thickness cuff tears progressed in size in 34% of cases, progressed to full-thickness tears in 7%, and did not progress in 59%. These imaging studies are further supported by histologic studies by Fukuda et al.,[27,28] who showed that spontaneous healing of partial-thickness tears appears to be unlikely except on rare occasions. In addition, Weber[29] showed that healing of partial-thickness rotator cuff tears after arthroscopic acromioplasty was not found on second-look arthroscopy.

Because degenerative tendon tissues and cells cannot be expected to contribute to healing,[12] furnishing an adequate number of cells with potential for tendon regeneration would be a pivotal part of biological approaches for rotator cuff regeneration. In this trial, we used autologous AD MSCs with proven safety in humans.[30] Experimental evidence has shown that AD MSCs would benefit tendon regeneration in various aspects because they prevented progression of tendon degeneration,[13] increased tensile strength and levels of type I collagen in tendon repair,[31] decreased fatty infiltration of muscle after repair,[32] mitigated the loss of bone mineral density of the humeral head in chronic tears,[33] and reduced the reinjury rate in racehorses.[34] Nonetheless, no clinical trials have been performed using AD MSCs for the treatment of rotator cuff tears except for our previous report.[10] The results

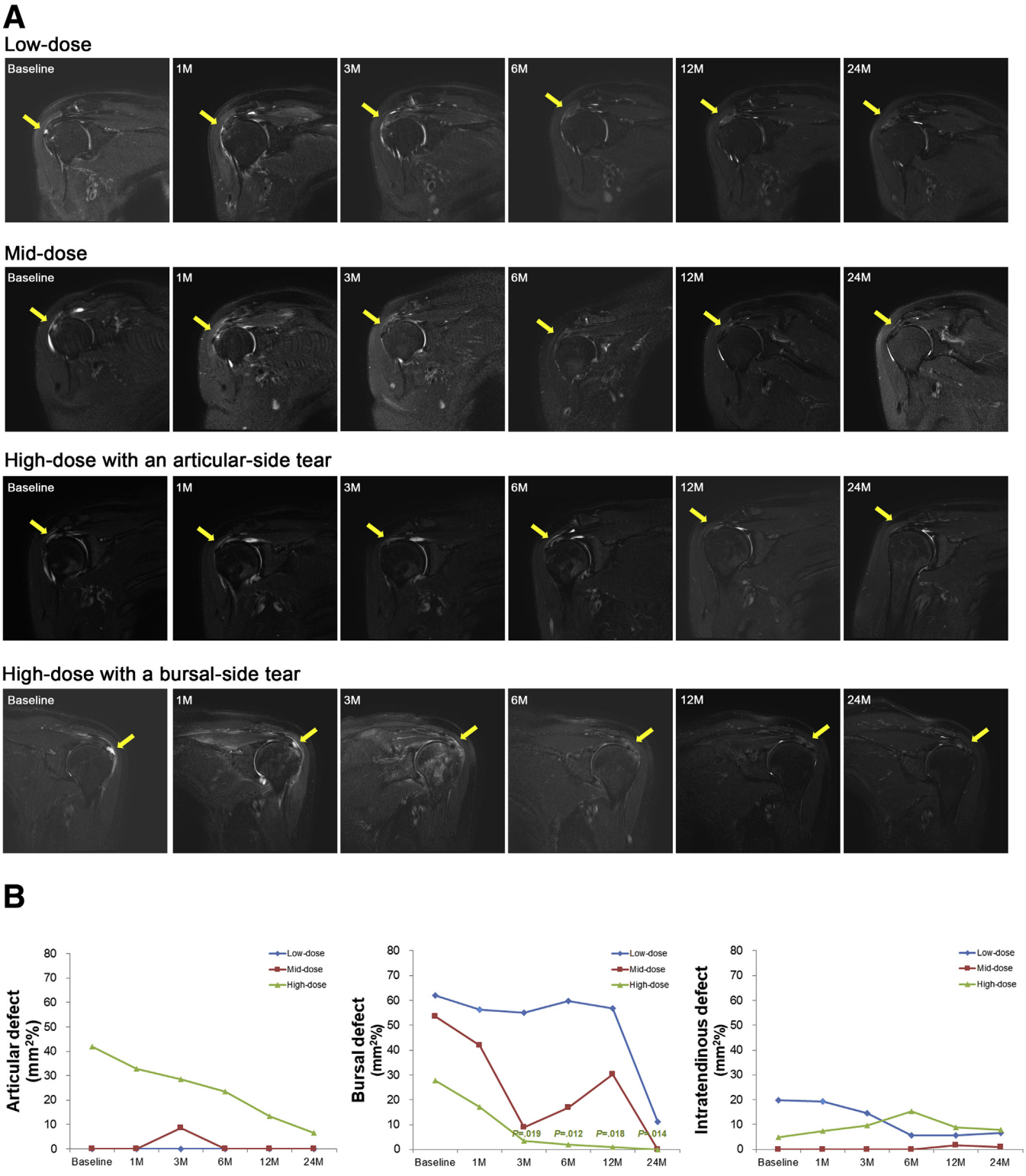

Figure 4. Changes in tendon defects of rotator cuff after intratendinous injection of adipose tissue–derived mesenchymal stem cells. (A) Oblique coronal magnetic resonance images. The yellow arrows indicate tendon defects. (B) Changes in volume of articular-sided, bursal-sided, and intratendinous tears. *P* values are for the high-dose group. Data up to 6 months are reprinted with permission.[10] (M, months.)

of the study showed that intratendinous injection of AD MSCs decreased defect size regardless of defect location: articular, bursal, or intratendinous. In particular, bursal-sided tears in the mid- and high-dose groups nearly disappeared at 1 year and did not recur at 2 years. Whereas statistical significance was

found only in the high-dose group, this finding was probably a result of the small numbers of participants rather than the small numbers of cells injected in the low- and mid-dose groups. Therefore, the continued promising clinical and structural results of this follow-up study would provide a strong impetus to investigate clearer mechanisms of AD MSCs for the treatment of rotator cuff disease as well as their more exact indications.

Limitations

There are several limitations to this study. First, the number of participants was small, and there was no control group. However, the results of this study should ensure a larger, randomized, controlled trial. Second, the heterogeneity of the tear types would be a concern for the establishment of exact treatment indications. Nonetheless, the preliminary results of the study showed that intratendinous injection of AD MSCs might be effective regardless of tear type. Third, the clinical and structural outcome measures used in this study might not be specific enough for evaluating outcomes of intratendinous injection of AD MSCs because, thus far, there has been no treatment that could improve pain and function via regeneration of tendon defects. Fourth, the exact mechanism of action of AD MSC injection was not elucidated because we still do not know how the regenerated tendon was formed. Histologic or in vivo imaging methods to track injected MSCs would be helpful. Fifth, the optimal cell dose is not clear yet. Many results in the low- and mid-dose groups were not statistically significant, unlike those in the high-dose group; however, this occurred because they were underpowered, not because the injections were actually ineffective. Further studies are necessary. Sixth, the postinjection protocol, including the period in which an abduction brace is worn, should be optimized. In this study, we chose a more conservative protocol that could be helpful for regeneration of tendon defects.

Conclusions

This study showed continued safety and efficacy of an intratendinous injection of AD MSCs for the treatment of partial-thickness rotator cuff tears over a 2-year period through regeneration of tendon defects.

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