Original Article

Associations of clinical outcomes and MRI findings in intra-articular administration of autologous adipose-derived stem cells for knee osteoarthritis

Junya Higuchi [a], Ryota Yamagami [a], Takumi Matsumoto [a, b], Tomohiro Terao [d], Keita Inoue [d], Shinsaku Tsuji [d], Yuji Maenohara [a], Tokio Matsuzaki [c], Ryota Chijimatsu [b], Yasunori Omata [a, b], Fumiko Yano [b], Sakae Tanaka [a], Taku Saito [a, *]

[a] Orthopaedic Surgery, Sensory and Motor System Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[b] Bone and Cartilage Regenerative Medicine, The University of Tokyo Hospital, Tokyo, Japan
[c] Japan Biodesign Program, Department of Cardiac Surgery, The University of Tokyo, Tokyo, Japan
[d] Avenue Cell Clinic, Tokyo, Japan

A B S T R A C T

Introduction: Clinical studies of intra-articular injection of mesenchymal stem cells for osteoarthritis (OA) indicate its efficacy. Here, we retrospectively investigated the associations of pretherapeutic magnetic resonance imaging (MRI) findings with the clinical outcomes up to 6 months, after intra-articular administration of adipose-derived stem cells (ASCs) to knee OA patients.
Methods: We first analyzed alterations of the visual analog scale (VAS) and knee injury and osteoarthritis outcome score (KOOS) in 57 knees of 34 patients from whom clinical scores were obtained before ASC therapy, and at 1, 3, and 6 months. Among the patients, we further examined MRI findings of 34 knees of 19 patients whose pretherapeutic MRI data were available.
Results: The mean improvement of VAS and KOOS-total during 6 months was 2.6 ± 4.0 (from 6.1 ± 2.5 to 3.5 ± 2.9, $P < 0.001$) and 10.2 ± 12.4 (from 54.4 ± 12.7 to 64.6 ± 13.8, $P < 0.01$), respectively. Scales related to pain and symptoms improved earlier than those related to activities of daily living (ADL) and sports/recreation. Improvement of VAS and KOOS-sports/recreation was significantly higher in patients with more severe cartilage lesions. Similarly, osteophyte lesions were associated significantly with improvement of VAS and KOOS-ADL, and BML was associated with KOOS-ADL and KOOS-sports/recreation.
Conclusions: In intra-articular administration of autologous ASCs for knee OA, improvement of VAS and KOOS-sports/recreation was significantly higher in patients with more severe cartilage lesions. Similarly, osteophyte lesions were associated significantly with improvement of VAS and KOOS-ADL, and BML was associated with KOOS-ADL and KOOS-sports/recreation. Clinical studies with larger numbers of patients and various kinds of data are necessary to predict therapeutic effects.

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1. Introduction

Osteoarthritis (OA) is a progressive joint disease involving mainly degeneration of articular cartilage and inflammation of the synovium, causing joint pain and significantly reducing motor functions. The epidemiology of OA is complicated and multifactorial, including biomechanical, genetic, and biological aspects. In adult articular cartilage, the regenerative capacity of chondrocytes is limited because of its avascular nature [1]. More than 10% of people aged >60 years suffer from pain due to OA [2]. Furthermore, the prevalence of OA, particularly in knee joints, increases with age [3].

For non-surgical management of OA, appropriate combinations of pharmacological and non-pharmacological interventions are recommended [4]. Pharmacological interventions include oral administration of non-steroidal anti-inflammatory drugs, acetaminophen, and duloxetine, and intra-articular injection of hyaluronic acid [4]. For non-pharmacological interventions, exercise, strength training, and weight management are widely recommended for various OA patients [4–9]. However, there are no effective therapeutic methods to modify OA progression at present. Surgical treatment, such as joint arthroplasty, is applied for patients who are resistant to these non-surgical therapies [10]. Although the clinical results are becoming generally satisfactory, many OA patients do not choose to undergo joint arthroplasty because of the invasiveness, risks, costs, and subsequent limitation of the joint motion range [11–13].

Intra-articular injection of mesenchymal stem cells (MSCs) has been attracting attention as a novel non-operative therapeutic method for OA. MSCs have been studied as a promising cell source for bone and cartilage regenerative medicine because of their multipotency. In recent years, critical effects, such as anti-inflammation, immunomodulation, and facilitation of tissue remodeling, have been focused on, and systemic administration of MSCs is applied for graft-versus-host disease and spinal cord injury [14–17]. In terms of OA, clinical trials of intra-articular injection of MSCs derived from bone marrow or subcutaneous adipose have been conducted worldwide, and many studies indicate its efficacy [18]. Jo et al. reported that intra-articular injection of autologous cultured adipose-derived stem cells (ASCs) improved the visual analog score (VAS) from 70 to 80 at the baseline to 30–50 at 1 year after injection [19]. Similar improvement of clinical scores at 6–12 months has been shown by other studies using ASCs [20,21]. In addition to the abovementioned effects, anti-apoptotic, anti-catabolic, anti-fibrotic, pro-chondrogenic, and pro-angiogenic effects are further proposed as the underlying mechanisms of MSC therapy [22]. However, most complete mechanisms remain unclear. Furthermore, associations of the pretherapeutic OA status with clinical outcomes of MSC therapy are unknown.

We began intra-articular administrations of cultured autologous ASCs to OA patients in June 2016 at the Avenue Cell Clinic in accordance with the Act on Securing Safety of Regenerative Medicine. Here, we retrospectively investigated the associations of pretherapeutic magnetic resonance imaging (MRI) findings with the clinical outcomes up to 6 months after the intra-articular administrations of ASCs to knee OA patients.

2. Materials & methods

2.1. Patient data collection of ASC therapy for knee OA

At the Avenue Cell Clinic, we performed intra-articular administrations of cultured autologous ASCs from June 2016. Inclusion criteria of the ASC therapy for knee OA were patients with grade 3–4 knee OA in the Kellgren–Lawrence classification [23] and patients with joint pain and stiffness that were resistant to other non-operative treatments. Exclusion criteria were patients unable to acquire consent for analysis, hypersensitivity to anesthetics used in adipose collection or substances used in the manufacturing process such as egg protein, an allergic reaction to penicillin, streptomycin, or amphotericin B used in cell culture, positive pathogenic microbiological tests including hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and syphilis, below the age of 20 years, pregnant or lactating women, complications with severe trauma, poor understanding of the therapy, and abnormal prothrombin time or activated partial thromboplastin time before treatment.

The present study retrospectively investigated knee OA patients who underwent ASC therapy. Among all 486 joints of 319 patients from June 2016 to December 2019, we first analyzed clinical score alterations of 57 knees of 34 patients from whom we obtained written informed consent after approval by the institutional ethics committee. Among the 57 knees of 34 patients, we examined MRI findings of 34 knees of 19 patients who underwent MRI before the ASC therapy and whose data were saved at the Avenue Cell Clinic. The study was approved by the institutional ethics committee using only the data of patients who provided written informed consent.

2.2. Preparation of ASCs

Abdominal subcutaneous adipose was transcutaneously collected under local anesthesia. The collected tissue was transferred immediately to the cell processing center (CPC) at the Avenue Cell Clinic. Cells were isolated from the tissue using an unwoven fabric and cultured in the optimized medium with 1%–4% autologous serum for 3–4 weeks up to about 1×10^8 cells at 37 °C with 5% CO_2.

2.3. Intra-articular injection of ASCs

Approximately 1×10^8 ASCs were injected into the medial tibiofemoral joint space, when the main lesion was located in the medial compartment, and into the lateral tibiofemoral joint space, when it was in the lateral compartment using a 23 G needle. We did not limit the joint motion or daily activity after the ASC therapy.

2.4. Clinical and imaging evaluation

VAS (0–10) and knee injury and osteoarthritis outcome score (KOOS; 0–100) were used to evaluate knee joint pain and functions. Both scores were obtained before the ASC therapy, and at 1, 3, and 6 months. For semi-quantitative evaluation of MRI findings, MRI osteoarthritis knee score (MOAKS) was used [24]. MOAKS assigns 2–4 grades for each structure including bone, cartilage, synovium, meniscus, ligament, tendon, and periarticular features. Periarticular features include pes anserine bursitis, iliotibial band signal, popliteal cyst, infrapatellar bursa signal, prepatellar bursa signal, and ganglion cyst. In this scoring system, the knee is divided into 14 articular subregions to score articular cartilage and bone marrow lesions (BMLs), and the subspinous region is included for BML scoring. Each pathological lesion is scored from 0 (normal) to 3 (severe).

2.5. Statistical analyses

Cluster analysis was performed on all elements of MOAKS from MRI data of all 34 knees of 19 patients. We used the Student's unpaired two-tailed *t*-test for comparisons between two groups. A *p*-value of less than 0.05 was considered statistically significant.

The analysis was performed using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan).

3. Results

3.1. Demographic data and adverse events

Among all patients, we analyzed clinical score alterations of 57 knees of 34 patients from whom clinical scores were obtained throughout the observation period. For associations of MRI findings with clinical outcomes, we further analyzed 34 knees of 19 patients whose pretherapeutic MRI data were saved at the Avenue Cell Clinic among the above 57 knees of 34 patients. Demographic data, period of cell culture, and the number of injected cells in both groups are shown in Table 1. There were no serious adverse events or complications during the observation period (Table 2). Effusion, joint pain, local heat, and stiffness were transient and completely improved in all patients within a few days to 1 week.

3.2. Clinical outcomes

VAS was significantly decreased at 1 month after the ASC injection and continued gradual improvement until 6 months (Fig. 1). The mean degree of the VAS improvement from the baseline to 6 months was 2.6 ± 4.0 (from 6.1 ± 2.5 to 3.5 ± 2.9, $P < 0.001$). Similar to VAS, KOOS-total improved, and the mean degree of the KOOS-total improvement from the baseline to 6 months was 10.2 ± 12.4 (from 54.4 ± 12.7 to 64.6 ± 13.8, $P < 0.01$) (Fig. 1). All subscales of KOOS showed improvement during 6 months (Fig. 1). Among VAS and KOOS subscales, VAS, KOOS-pain, KOOS-symptom, and KOOS-quality of life (QOL) improved mostly in the 1 month, while KOOS-activities of daily living (ADL) and KOOS-sports improved gradually (Fig. 1).

We next compared the improvement rates of these clinical scales during the observation period. For VAS, KOOS-pain, and KOOS-symptom, 70%—80% improvement was achieved at 1 month (Fig. 2). The improvement rates decreased in the order of KOOS-QOL, KOOS-ADL, and KOOS-sports/recreation (Fig. 2).

3.3. Evaluation of pretherapeutic MRI findings

MOAKS was obtained from pretherapeutic MRI findings in the 34 knees of 19 patients (Table 3). To determine correlations between the lesions, we performed cluster analysis. First, surrounding structures, such as meniscal lesions, synovitis, and periarticular lesions, were distinguished from other lesions (Fig. 3). Next, size and the number of BMLs were classified from cartilage loss, ligament/tendon lesions, and osteophytes (Fig. 3). According to the cluster analysis, we named the three MOAKS clusters as (1) bone, (2) cartilage and connective structures, and (3) surrounding structures as shown in Fig. 3.

3.4. Associations of clinical outcomes with pretherapeutic MRI findings

We first set the minimally clinical important difference (MCID) of VAS as 2.0 according to previous studies [25—27] and divided the

Table 2
Rates of adverse events during 6 months after injection.

	34 patients (57 knees)
Effusion	6 (11.5%)
Pain	5 (9.6%)
Local heat	1 (1.9%)
Stiffness	1 (1.9%)
Infection	0 (0%)

34 knees of 19 patients with MRI data into two groups: improved and poorly improved groups. Similarly, the MCIDs of KOOS-total, -pain, -symptoms, -ADL, -sports/recreation, and -QOL were set as 10.0, 13.4, 15.5, 15.4, 19.6, and 21.1, respectively, according to a previous study [28]. MOAKSs in the two groups for each scale are shown in Table 3. For VAS, scores for the size of cartilage loss and osteophyte lesions were significantly higher in the improved group (Table 3). Scores for the BML size and osteophyte lesions were significantly higher in the improved group of KOOS-ADL, and those for the BML size, cartilage loss size, and ratio of full-thickness cartilage loss were significantly higher in the improved group of KOOS-sports/recreation (Table 3). No MOAKS was associated with improvement of KOOS-total, -symptom, -pain, and QOL (Table 3).

We next analyzed associations of the clinical outcomes with the MOAKS clusters. A bone lesion was significantly associated with KOOS-ADL (Table 4). A lesion of the cartilage and connective structures was significantly associated with VAS, KOOS-ADL, and KOOS-sports/recreation (Table 4). A lesion of the surrounding structures was not associated with all scales (Table 4).

3.5. Associations of clinical outcomes with other factors

In addition to pretherapeutic MRI findings, we analyzed the effects of other factors including age of patients, culture period, and the number of injected cells. There were no significant associations between all scales and these factors (Table 5).

3.6. Case series with post-therapeutic MRI data

We finally analyzed four cases who additionally underwent MRI at 6 months after ASC injection. Patient 1, 74-year-old female, and Patient 2, 65-year-old male, had advanced OA with BML and cartilage loss (Fig. 4, Table 6). Their clinical symptoms improved throughout the period (Table 7), but the lesions were not changed obviously except for BMLs in the MRI at 6 months after ASC injection (Fig. 4, Table 6). Patient 3, 55-year-old male with similar grade OA did not display clinical improvement, although BML was decreased and the size of the medial meniscus was increased (Fig. 4, Tables 6 and 7). Patient 4, 54-year-old male, displayed an increased BML in the after MRI 6 months, but his clinical symptoms have improved (Fig. 4, Tables 6 and 7).

4. Discussion

The present study investigated the clinical outcomes of intra-articular administration of ASCs to knee OA patients up to 6 months, and the associations of pretherapeutic MRI findings with

Table 1
Demographic data of the evaluated patients. Data are shown as the mean $\pm$ SD. M, male; F, female; MRI, magnetic resonance imaging.

	Sex	Age (years)	Culture period (days)	Number of injected cells
Total (34 patients)	M: F = 10 : 24	67.5 ± 11.1	32.0 ± 8.9	$8.26 \pm 4.62 \times 10^7$
Patients with MRI (19 patients)	M: F = 5 : 14	69.5 ± 9.9	30.5 ± 8.6	$7.64 \pm 4.18 \times 10^7$
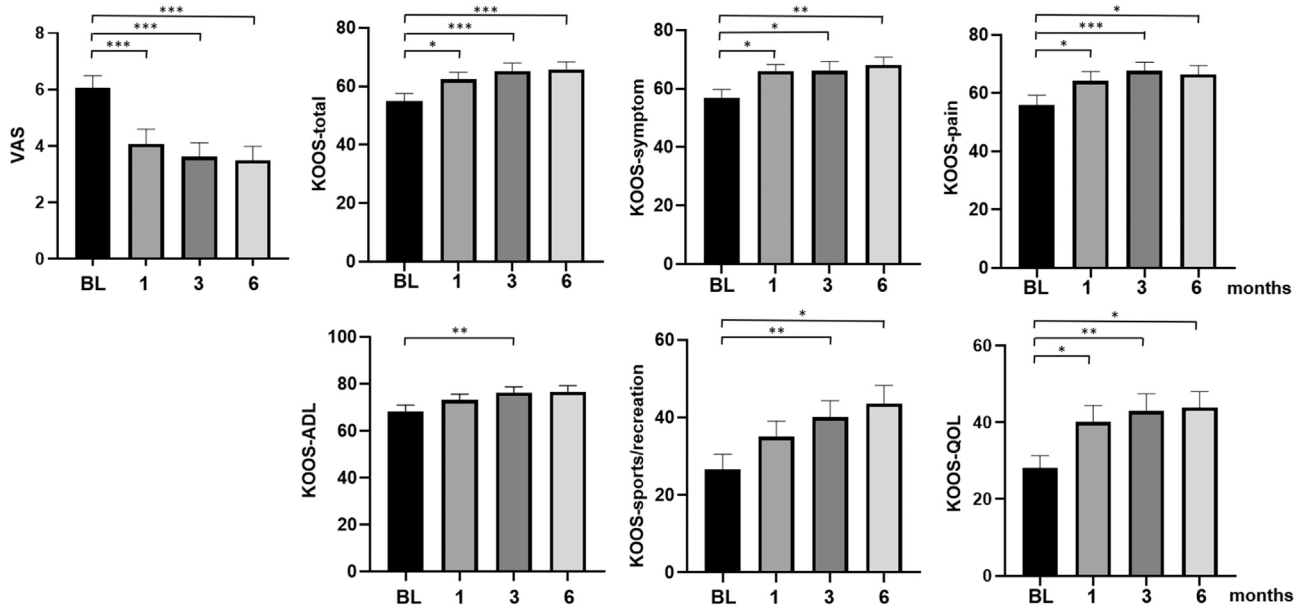
Fig. 1. Alterations of clinical scores. Visual analog scale (VAS), total and subscales of knee injury and osteoarthritis outcome score (KOOS) at baseline (BL), and 1, 3, and 6 months after injection are shown. All data are shown as the mean ± SE. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. ADL, activities of daily living; QOL, quality of life.

the clinical outcomes. Alterations of VAS and subscales of KOOS were similar to previous studies of intra-articular injection of autograft MSCs derived from bone marrow and adipose tissue [19–21,29]. First, we hypothesized that improvement of these clinical scores would be significantly higher in OA patients with milder lesions. However, interestingly, analyses of associations between MOAKS and the clinical outcomes indicated the opposite trend. The improved group in VAS had more severe lesions in their articular cartilage and osteophyte (Table 3). These lesions in cartilage and connective structures affect improvement of KOOS-ADL and KOOS-sports/recreation (Tables 3 and 4). The presence or

severity of BML were associated only with KOOS-ADL and KOOS-sports/recreation, and not with scales that are directly related to pain and symptoms (Table 3). Lesions of the meniscus, ligament, tendon, and synovium are involved in OA pathogenesis [30], but they were not associated with improvement of all scales (Table 3). These data imply that the ASC therapy provided some beneficial effects for OA patients with advanced lesions. Meanwhile, patient satisfaction scores were not included in the present study. Some patients with severe pain before treatment may be unsatisfied with the ASC therapy because of remaining pain or symptoms. A larger
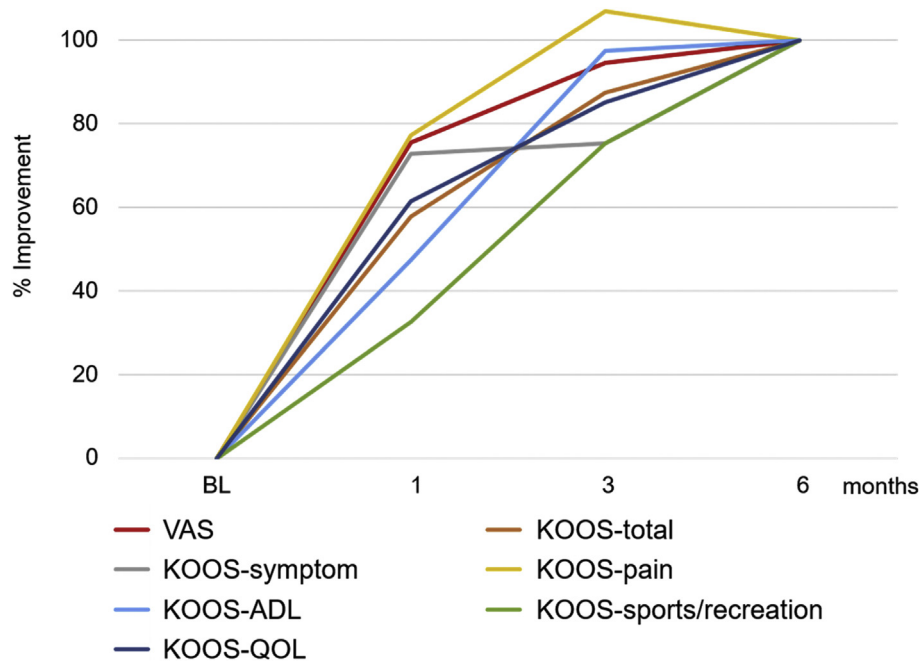
Fig. 2. Improvement rates of clinical scores during the 6 months after injection.

Table 3

Associations of clinical outcomes with pretherapeutic MRI findings. MRI osteoarthritis knee scores (MOAKSs) for each lesion in the improved and poorly improved groups for each clinical scale are shown. In each scale, 34 knees of 19 patients were divided into two groups in each scale, namely improved and poorly improved groups according to minimally clinical important difference (MCID) for each scale. MCIDs of VAS, KOOS-total, KOOS-symptoms, KOOS-pain, KOOS-ADL, KOOS-sports/recreation, and KOOS-QOL were set as 2.0, 10.0, 13.4, 15.5, 15.4, 19.6, and 21.1, respectively. All data are shown as the mean ± SD. *$P < 0.05$. BML, bone marrow lesion.

| Lesion (Range of score)	Mean value in total group	VAS Improved	VAS Poorly improved	VAS P value	KOOS-total Improved	KOOS-total Poorly improved	KOOS-total P value	KOOS-symptom Improved	KOOS-symptom Poorly improved	KOOS-symptom P value	KOOS-pain Improved	KOOS-pain Poorly improved	KOOS-pain P value	KOOS-ADL Improved	KOOS-ADL Poorly improved	KOOS-ADL P value	KOOS-sports/recreation Improved	KOOS-sports/recreation Poorly improved	KOOS-sports/recreation P value	KOOS-QOL Improved	KOOS-QOL Poorly improved	KOOS-QOL P value
Size of BML including cysts (0−51)	8.1 ± 4.4	8.9 ± 4.4	7.0 ± 4.4	0.21	8.7 ± 4.8	7.6 ± 4.2	0.46	8.6 ± 5.4	7.9 ± 4.1	0.72	7.7 ± 4.7	8.4 ± 4.3	0.63	10.6 ± 3.7	7.2 ± 4.4	*0.04	9.9 ± 3.8	6.7 ± 4.5	*0.04	9.1 ± 5.4	7.7 ± 4.0	0.40
Raito of BML vs cysts (0−51)	17.8 ± 8.3	18.7 ± 8.7	16.6 ± 7.8	0.46	18.7 ± 9.3	17.1 ± 7.6	0.59	17.9 ± 10.6	17.8 ± 7.5	0.97	16.7 ± 8.9	18.7 ± 7.9	0.49	22.2 ± 6.1	16.2 ± 8.5	0.06	20.6 ± 6.9	15.6 ± 8.8	0.08	18.3 ± 10.1	17.6 ± 7.6	0.82
Number of BML (0−51)	7.6 ± 3.9	8.4 ± 4.4	6.7 ± 3.1	0.23	7.8 ± 4.1	7.5 ± 3.9	0.84	8.3 ± 4.9	7.4 ± 3.6	0.55	7.1 ± 4.1	8.1 ± 3.8	0.50	9.6 ± 3.5	7.0 ± 3.9	0.09	8.9 ± 3.5	6.7 ± 4.0	0.11	9.3 ± 5.5	7.0 ± 2.9	0.11
Size of cartilage loss (0−42)	32.4 ± 6.1	34.6 ± 5.4	30.0 ± 6.1	*0.02	33.4 ± 6.2	31.7 ± 6.1	0.42	31.7 ± 7.3	32.7 ± 5.8	0.66	32.3 ± 6.6	32.6 ± 5.9	0.89	34.2 ± 4.6	31.8 ± 6.5	0.32	35.6 ± 3.7	29.9 ± 6.7	*0.01	32.3 ± 7.1	32.5 ± 5.8	0.93
Ratio of full-thickness cartilage loss (0−42)	19.6 ± 7.8	20.9 ± 9.3	18.0 ± 5.1	0.28	20.3 ± 9.3	19.2 ± 6.5	0.69	18.3 ± 11.6	20.1 ± 6.1	0.56	19.5 ± 9.4	19.7 ± 6.4	0.94	23.4 ± 5.7	18.3 ± 8.0	0.09	22.5 ± 5.4	17.4 ± 8.7	*0.03	19.2 ± 11.2	19.8 ± 6.1	0.83
Osteophyte (0−36)	22.7 ± 7.2	24.4 ± 8.0	20.5 ± 5.6	*0.03	25.0 ± 7.5	20.8 ± 6.7	0.10	24.4 ± 9.0	22.0 ± 6.6	0.40	24.5 ± 7.5	21.3 ± 6.9	0.20	28.9 ± 4.7	20.4 ± 6.7	*0.002	24.9 ± 6.0	20.9 ± 7.8	0.11	24.5 ± 8.5	21.9 ± 6.7	0.35
Meniscus (0−12)	6.0 ± 2.9	6.1 ± 3.2	5.9 ± 2.5	0.81	5.9 ± 2.6	6.1 ± 3.2	0.91	5.6 ± 2.0	5.0 ± 1.6	0.44	5.8 ± 2.6	6.2 ± 3.1	0.72	6.3 ± 2.8	5.9 ± 2.9	0.69	5.9 ± 2.6	5.6 ± 2.7	0.80	5.7 ± 1.9	5.0 ± 1.5	0.25
Ligament/tendon (0−15)	5.2 ± 1.7	5.6 ± 1.8	4.6 ± 1.4	0.08	5.5 ± 1.7	4.9 ± 1.6	0.28	5.0 ± 2.3	6.4 ± 3.0	0.23	5.7 ± 1.7	4.8 ± 1.6	0.13	5.9 ± 1.6	4.9 ± 1.7	0.14	5.8 ± 1.6	4.7 ± 1.6	0.06	5.1 ± 2.2	6.4 ± 3.1	0.24
Synovitis (0−6)	3.3 ± 1.1	3.3 ± 1.2	3.3 ± 1.0	0.96	3.3 ± 1.0	3.4 ± 1.2	0.79	2.8 ± 0.8	3.5 ± 1.1	0.08	3.1 ± 0.8	3.5 ± 1.3	0.23	3.0 ± 0.9	3.4 ± 1.2	0.31	3.2 ± 1.1	3.3 ± 1.1	0.87	2.8 ± 0.8	3.5 ± 1.1	0.07
Periarticular features (0−6)	3.0 ± 1.3	3.3 ± 1.2	2.7 ± 1.4	0.16	3.3 ± 1.2	2.8 ± 1.5	0.37	2.9 ± 1.2	3.1 ± 1.4	0.72	3.3 ± 1.2	2.8 ± 1.4	0.37	3.3 ± 1.3	2.9 ± 1.4	0.43	3.2 ± 1.2	2.9 ± 1.5	0.59	2.8 ± 1.1	3.1 ± 1.4	0.53
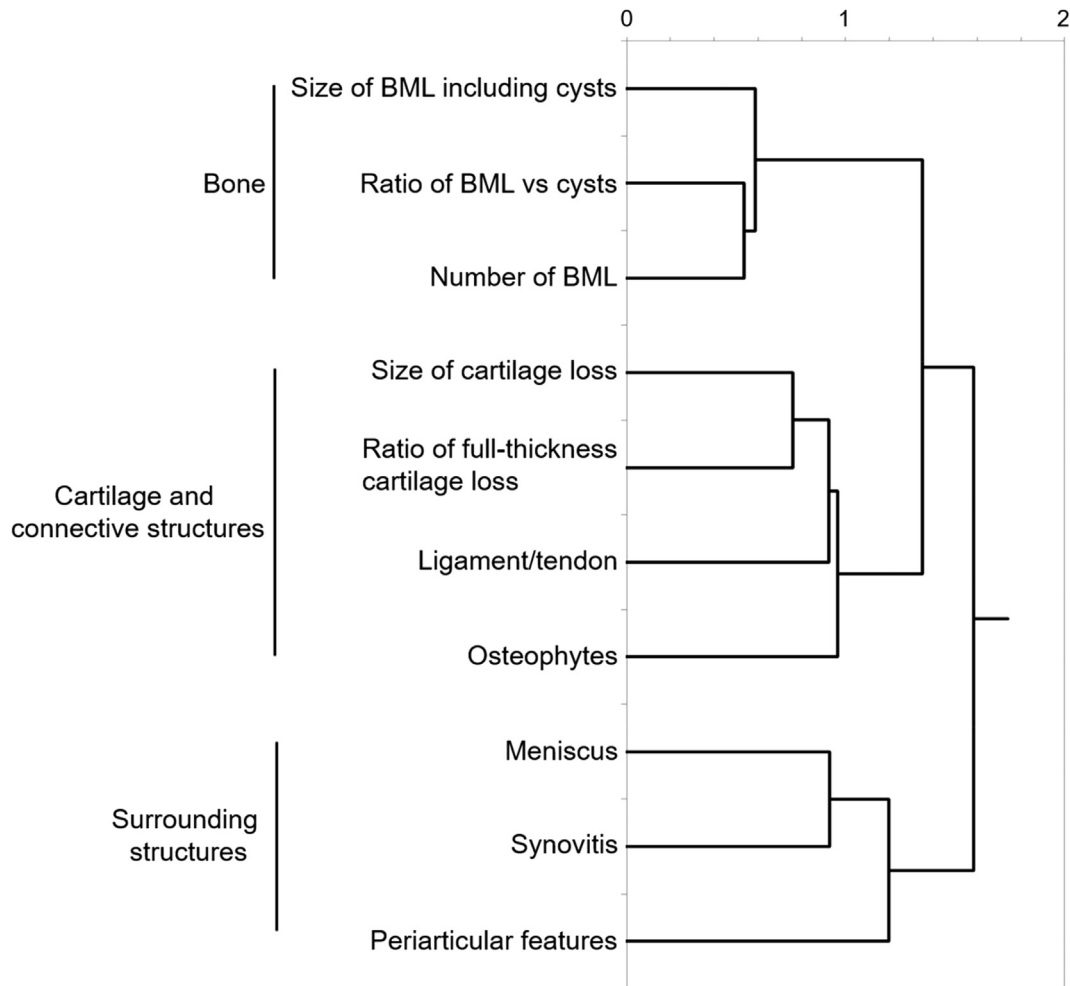
Fig. 3. Clustering analysis based on the scores of MOAKS elements.

number of patients are necessary to further analyze associations of pretherapeutic MRI findings with clinical outcomes.

Although many studies have shown positive and satisfactory results, the underlying molecular mechanisms are not well understood [31,32]. In addition to the capacities for proliferation and multipotent differentiation, more attention has recently been focused on the immunomodulatory, anti-inflammatory, and tissue-repairing effects of MSCs. These effects appear to contribute to beneficial modulation of OA pathophysiology. Many clinical studies have demonstrated improvement of pain and symptoms in OA patients by intra-articular injection of MSCs. However, their significant effects on structural improvement, such as regeneration of articular cartilage or the meniscus, have not been proven. Notably, reduction of a cartilage defect or an increase in the degenerated meniscus was observed in some patients, although these effects were not significant in all patients [19]. At present, we do not know why structural improvement occurs in some patients and not in others, and we cannot predict such improvements. Interestingly, BML was decreased and the size of the meniscus was increased in Patient 3 (Fig. 4, Tables 6 and 7). However, the clinical scores did not improve. Conversely, pain and symptoms improved well in Patient 4, although structural improvement was not observed (Fig. 4, Tables 6 and 7). Taken together, the beneficial effects of MSC therapy for OA are probably due to anti-inflammatory effects and not tissue repair.

Despite the efficacy of MSC therapy for OA shown by many clinical studies, it is still difficult to draw robust conclusions because of the small numbers of patients, short observation period, lack of appropriate controls, or other issues in study designs. In Japan, since the enforcement of the Act on Securing Safety of Regenerative Medicine in 2014, autologous MSCs are applicable to various diseases under required inspection and regulation. Because of its efficacy, intra-articular administration of autologous ASCs for OA has gradually increased in recent years. ASC therapy for OA is not covered by public health insurance and is now performed mostly in private clinics equipped with a CPC. Perhaps because of these situations, funding and execution of strict clinical studies such as randomized placebo-controlled trials of this therapy may be difficult in Japan. However, a number of clinical studies using allografted ASCs for OA are now ongoing worldwide. The application of allografted ASCs may make it easier to perform these promising studies in the near future.

In the present study, we examined associations of pretherapeutic MRI findings with clinical outcomes after ASC therapy. Considering that structural improvement may not be essential for improvement of pain and symptoms, information from imaging only may be insufficient for accurate prediction of therapeutic effects. For example, biochemical examination of blood and synovial fluid may provide novel findings. Further understanding of the

Table 4

Associations of clinical outcomes with MOAKS clusters. Scores of the three MOAKS clusters in the improved and poorly improved groups for each clinical scale are shown. In each scale, 34 knees of 19 patients were divided into the two groups identically to Table 3. All data are shown as the mean ± SD. *$P < 0.05$.

Lesion (Range of score)	Mean value in total group	VAS			KOOS-total			KOOS-symptom			KOOS-pain			KOOS-ADL			KOOS-sports/recreation			KOOS-QOL		
		Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value
Bone (0−153)	33.5 ± 15.8	36.1 ± 16.6	30.3 ± 14.6	0.30	35.2 ± 17.5	32.2 ± 14.6	0.59	33.9 ± 18.5	32.9 ± 9.8	0.87	31.5 ± 17.1	35.2 ± 14.9	0.51	42.3 ± 12.1	30.4 ± 15.9	*0.04	39.3 ± 28.0.9	28.9 ± 16.4	0.06	36.7 ± 20.1	32.2 ± 13.9	0.46
Cartilage and connective structures (0−135)	79.9 ± 19.5	85.5 ± 22.1	72.9 ± 13.3	*0.02	84.2 ± 22.8	76.6 ± 16.4	0.27	82.2 ± 21.2	75.8 ± 16.1	0.36	81.9 ± 23.3	78.4 ± 16.5	0.60	92.4 ± 14.6	75.4 ± 19.3	*0.02	88.8 ± 13.6	72.9 ± 20.9	*0.02	81.7 ± 27.4	79.2 ± 15.9	0.74
Surrounding structures (0−24)	12.4 ± 4.3	12.7 ± 4.3	11.9 ± 4.2	0.56	12.5 ± 3.5	12.3 ± 4.9	0.89	12.2 ± 3.7	12.6 ± 5.3	0.82	12.1 ± 3.3	12.5 ± 5.0	0.79	12.7 ± 3.5	12.2 ± 4.6	0.80	12.3 ± 3.7	11.8 ± 4.5	0.76	10.7 ± 2.6	13.0 ± 4.6	0.15

Table 5

Associations of clinical outcomes with other factors. The age of patients, cell culture period, and number of injected cells in the improved and poorly improved groups for each clinical scale are shown. In each scale, 34 knees of 19 patients were divided into the two groups identically to Table 3. All data are shown as the mean ± SD.

	Mean value in total group	VAS			KOOS-total			KOOS-symptom			KOOS-pain			KOOS-ADL			KOOS-sports/recreation			KOOS-QOL		
		Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value	Improved	Poorly improved	P value
Age (years)	67.5 ± 11.1	70.4 ± 8.8	66.6 ± 11.7	0.31	68.8 ± 9.2	70.3 ± 10.8	0.71	66.8 ± 14.4	67.9 ± 8.8	0.79	69.3 ± 10.2	69.3 ± 9.1	0.99	69.9 ± 7.8	69.1 ± 10.1	0.84	68.8 ± 8.0	69.6 ± 10.6	0.82	67.0 ± 5.4	70.3 ± 10.7	0.39
Culture period (days)	31.6 ± 8.9	33.3 ± 11.1	30.2 ± 6.3	0.36	34.1 ± 12.3	29.4 ± 4.7	0.21	31.9 ± 9.9	31.8 ± 8.6	0.97	34.5 ± 11.5	30.1 ± 6.9	0.23	33.9 ± 12.1	31.5 ± 8.4	0.55	32.7 ± 9.8	31.8 ± 9.4	0.80	35.3 ± 12.5	30.6 ± 7.5	0.22
Number of injected cells (× 107 cells)	8.2 ± 4.6	7.8 ± 3.7	9.4 ± 5.2	0.32	7.7 ± 4.1	9.0 ± 5.3	0.45	9.3 ± 4.9	7.8 ± 4.3	0.34	7.8 ± 4.1	9.0 ± 5.3	0.53	9.2 ± 4.2	8.1 ± 5.0	0.58	6.9 ± 2.2	9.5 ± 5.8	0.14	9.7 ± 5.4	7.8 ± 4.4	0.32
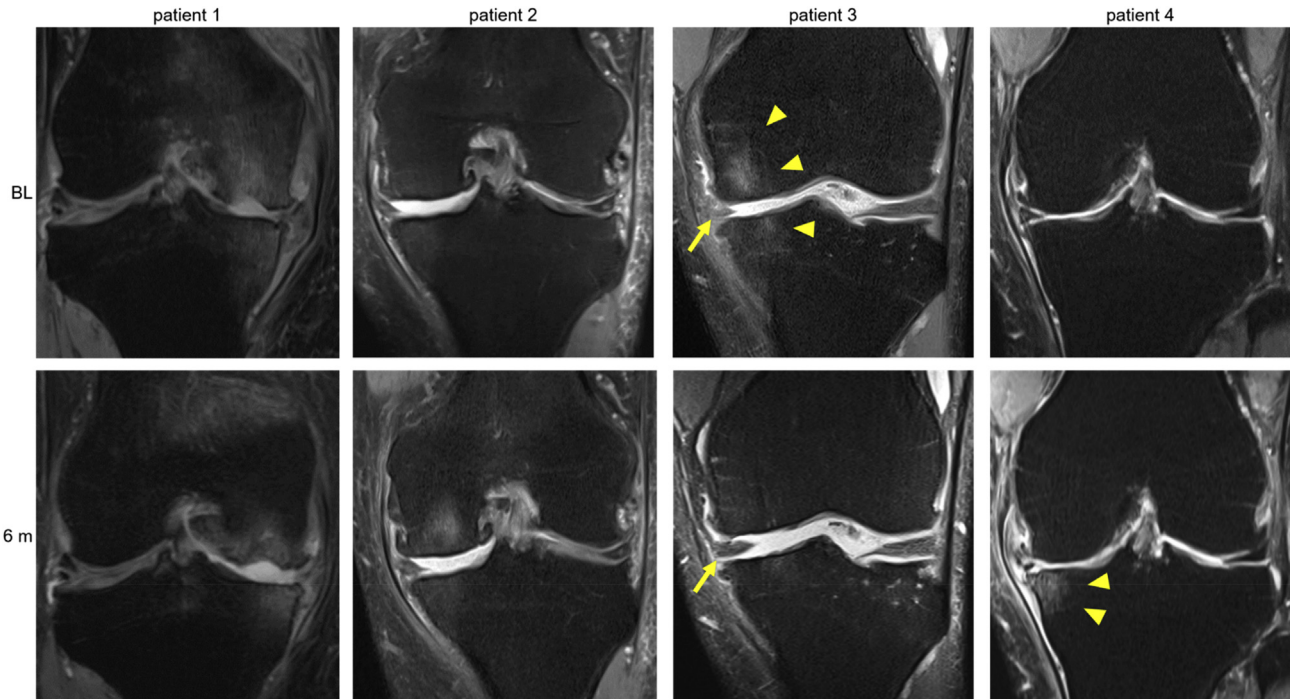
Fig. 4. MRI images of four patients before and at 6 months after injection. Patient 1, 74-year-old female; Patient 2, 65-year-old male; Patient 3, 55-year-old male; Patient 4, 54-year-old male. Yellow arrows and arrowheads indicate the medial meniscus and BML, respectively.

Table 6
Changes of MOAKSs in Patient 1, 74 years old female; Patient 2, 65 years old male; Patient 3, 55 years old male; and Patient 4, 54 years old male.

	Patient 1		Patient 2		Patient 3		Patient 4	
Lesion (range of score)	BL	6 m	BL	6 m	BL	6 m	BL	6 m
Size of BML including cysts (0 51)	17	8	17	8	11	8	10	7
Raito of BML vs cysts (0 51)	20	19	20	19	31	18	27	27
Number of BML (0 51)	7	7	7	7	11	9	9	7
Size of cartilage loss (0 42)	31	33	31	33	37	38	37	39
Ratio of full-thickness cartilage loss (0 42)	19	21	19	21	26	23	28	29
Osteophyte (0 36)	16	16	16	16	28	29	21	22
Meniscus (0 12)	8	9	8	9	6	6	9	9
Ligament/tendon (0 15)	3	3	3	3	5	4	4	3
Synovitis (0 6)	4	3	4	3	3	3	5	4
Periarticular features (0 6)	4	4	4	4	3	3	3	3

Table 7
Changes of clinical scores in Patient 1, 74 years old female; Patient 2, 65 years old male; Patient 3, 55 years old male; and Patient 4, 54 years old male.

	Patient 1				Patient 2				Patient 3				Patient 4			
	BL	1	3	6 m	BL	1	3	6 m	BL	1	3	6 m	BL	1	3	6 m
VAS	6.4	2.9	2.5	1.1	7.2	2.5	2.1	2.9	3.2	3.0	2.5	2.6	8.8	4.8	2.5	2.0
KOOS-total	72.6	78.6	89.3	95.8	45.8	57.7	64.3	51.2	67.3	56.0	63.7	60.7	63.7	61.3	74.4	76.8
KOOS -symptom	75.0	78.6	85.7	85.7	57.1	75.0	60.7	67.9	75.0	60.7	67.9	75.0	78.6	46.4	53.6	75.0
KOOS-pain	69.4	80.6	83.3	91.7	41.7	58.3	61.1	41.7	75.0	72.2	72.2	72.2	52.8	58.4	64.4	72.2
KOOS-ADL	82.4	86.8	92.7	100	54.4	70.6	75.0	66.2	76.5	61.8	77.9	72.1	82.4	82.4	89.7	88.2
KOOS-sports/recreation	55.0	55.0	100	100	25.0	15.0	50.0	20.0	40.0	25.0	25.0	15.0	30.0	30.0	65.0	65.0
KOOS-QOL	56.3	68.8	81.3	100	25.0	25.0	50.0	18.8	31.3	25.0	25.0	18.8	25.0	43.8	68.8	56.3

molecular mechanisms underlying ASC therapy for OA is indispensable for such prediction, and non-clinical studies using animal models should also be performed for this purpose.

5. Conclusion

In intra-articular administration of autologous ASCs for knee OA, improvement of VAS and KOOS-sports/recreation was significantly higher in patients with more severe cartilage lesions. Similarly, osteophyte lesions were significantly associated with improvement of VAS and KOOS-ADL, and BML was associated with KOOS-ADL and KOOS-sports/recreation. Clinical studies with larger numbers of patients and various kinds of data are necessary to predict the therapeutic effects.

Declaration of Competing Interest

Acknowledgments

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