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Original Article

Comparison of patient-reported outcomes of treatment with low- and intermediate molecular weight hyaluronic acid in Japanese patients with symptomatic knee osteoarthritis: A prospective, randomized, single-blind trial

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ABSTRACT

Objectives: The objective of this study was to compare the clinical outcomes of treatment with low- or intermediate-molecular-weight hyaluronic acid (HA) in patients with knee osteoarthritis (OA).
Methods: In total, 59 patients with OA who fulfilled the criteria of the American College of Rheumatology for OA were enrolled. Patients were randomly assigned in a 1:1 ratio to the low- or intermediate-molecular-weight HA group. An intraarticular injection of HA into the knee joint was performed five times per week. The visual analog scale for pain (pain VAS) and Japanese Knee Osteoarthritis Measure (JKOM) score were analyzed at baseline and week 6 to assess the outcomes.
Results: Pain VAS and JKOM score were significantly improved in both groups. At follow-up, there were no significant between-group differences in pain VAS or total JKOM score. Moreover, reduction in pain VAS and JKOM score was not significantly different between the two groups.
Conclusions: Both low- and intermediate-molecular-weight HA have significant efficacy in the first-line treatment of patients with knee OA as indicated by patient-reported outcomes. However, there does not appear to be any difference between the efficacy of low- and intermediate-molecular-weight HA as indicated by the JKOM score. We believe that the results of this study provide important insights into the clinical management of Japanese patients with knee OA.
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Introduction

Knee osteoarthritis (OA) is a serious, progressive joint disorder that is characterized by cartilage degeneration and inflammation.[1,2] The incidence of OA has been increasing in the elderly population. In Japan, the prevalence of knee OA increases with age.[3] There are several non-surgical options for the management of OA such as administration of nonsteroidal anti-inflammatory drugs, intra-articular injection (IA) of corticosteroids or hyaluronic acid (HA), exercise, and cognitive behavioral therapy. Current Osteoarthritis Research Society International (OARSI) guidelines recommend the use of IA-HA based on level 1B evidence.[4]

This approach replenishes the declining concentration and viscoelasticity of the synovial fluid in knee, effectively reducing the pain and improving the function of knee, with concomitant improvement in quality of life, as demonstrated by systematic reviews and meta-analyses.[5–7] The comparison results of efficacy of IA between HA and placebo in meta-analysis were as follows: the effect sizes were 0.17 (95% confidence interval [95% CI], 0.12–0.22) at month 1, 0.21 (95% CI, 0.15–0.28) at month 2, and 0.30 (95% CI, 0.25–0.35) at month 3. The HA was observed to favor all time point.[5] Moreover, the comparison results of the efficacy of IA between HA and corticosteroids in another meta-analysis were as follows: the effect sizes at week 2, 4, 8, and 12 were seen to favor corticosteroids, equal, HA, and HA, respectively.[6]

HA is classified into low- (500–730 kDa), intermediate- (800–2000 kDa), and high- (average: 6000 kDa) molecular-weight species.[8] In previous report, synovial fibroblasts derived from a

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joint with OA responded to stimulation with preparations of average-molecular-weight HA in a concentration dependent manner.[9] Although IA of high-molecular-weight HA for the treatment of knee OA was effective in the reduction of pain and improvement of physical function, it was often discontinued due to adverse events.[10–12] Therefore, in Japan, IA of low- and intermediate-molecular-weight HA is commonly used for the treatment of knee OA. However, to the best of our knowledge, there have been no studies comparing the clinical outcomes of the treatment with low- and intermediate-molecular-weight HA in Japanese patients with knee OA.

The aim of this study was, therefore, to compare the clinical outcomes of treatment with low- and intermediate-molecular-weight HA in patients with moderate knee OA. We hypothesized that the molecular weight of HA affects the clinical outcomes.

Methods

Study design

This trial was a prospective, randomized, single-blind trial that aimed to clarify the efficacy of two different molecular-weight HA species for the treatment of knee OA. Patients were randomized in a 1:1 ratio into a low- or intermediate-molecular-weight HA group by the clinical research center of the authors' affiliated institution. Patients were blinded to the group they were assigned to. Clinical outcomes of the patients were compiled by medical staff who were blinded to patient characteristics and group. The primary endpoint was an efficacy of visual analog scale for pain (pain VAS).

All patients provided written informed consent after receiving an explanation of the study protocol. The study and all its protocols were approved by the Institutional Review Board of the authors' affiliated institution (approval number: TGE00847-064), and the study was conducted according to the principles of the Declaration of Helsinki.

Patients

The patients who were diagnosed with knee OA were outpatients of the authors' affiliated institution, aged ≥40 years and consecutively enrolled when informed consent was obtained. We recruited patients who fulfilled the criteria of the American College of Rheumatology for knee OA.[13] Severity of knee OA was classified according to the Kellgren-Lawrence (K/L) grade[14]: it was assessed using anteroposterior radiographs that were taken with patients in the standing position just prior to treatment. Moreover, the patients had a history of knee pain for at least 3 months. Exclusion criteria were existence of symptoms bilaterally, previous arthroplasty of weight-bearing joints, secondary knee OA, and history of treatment for trauma of the knee and knee OA. Moreover, the patients with joint effusion were excluded in this study because the results of pain and symptoms are affected by aspiration of joint effusion.[15]

Treatment regimen

Patient received treatment using with either low-molecular-weight HA (500–1200 kDa; Artz®, Seikagaku, Tokyo, Japan) or intermediate-molecular-weight HA (1500–3900 kDa; Suvenyl®, Chugai, Tokyo, Japan). The HA was administered via IA into the knee joint once a week over a period of 5 weeks. No other treatment was administered.

Assessment of clinical results

We recorded the pain VAS and Japanese Knee Osteoarthritis Measure (JKOM) score. Pain VAS was recorded on a scale of 0–100 mm; JKOM score is a patient-reported outcome comprising 25 questions in four subcategories: pain and stiffness (0–32), activities of daily living (0–40), social activities (0–20), and general health (0–8), with maximum score of 100 points.[16] Pain VAS and JKOM score were measured at baseline and week 6.

Statistical analysis

Between-group comparisons of patient demographics and clinical characteristics at baseline and follow-up were performed using Mann–Whitney U test and Fisher's exact test for the following variables: age; sex; disease duration; body mass index; K/L grade; pain VAS; total, pain and stiffness, activities of daily living, social activities, and general health JKOM score; and rate of responder in pain VAS. Pain VAS, and total, pain and stiffness, activities of daily living, social activities, and general health JKOM scores were compared between baseline and follow-up for both groups using a paired *t*-test. The responder in pain VAS was defined a decrease of at least 20% and at least 10 mm.[17]

Statistical significance was accepted at a p-value of <0.05. The result of power analysis was 0.85 in this study. All analyses were performed using the R Statistical Package, version 3.3.2 (http://www.r-project.org/).

Results

A total of 59 eligible patients were enrolled in the present study (Fig. 1). Patient demographics and clinical characteristics at baseline for both groups are shown in Table 1. There were no significant between-group differences in any variables at baseline.

Clinical outcomes at baseline and for two groups were shown in Table 2. Both groups exhibited significant improvements in all variables.

There was no significant difference in pain VAS or total JKOM score at follow-up between the low- and intermediate-molecular-weight HA groups ($p = 0.278$ and 0.451, respectively). There was no significant difference in the scores of pain and stiffness, activities of daily living, and social activities at follow-up between the two groups ($p = 0.278$ and 0.451, respectively). The general health score was significantly difference between the two groups ($p = 0.030$).

Pain VAS and total JKOM score were reduced in both groups compared with those at baseline by 42.6 ± 65.3% and 45.7 ± 38.3% (pain VAS) for the low- and intermediate-molecular-weight HA groups, respectively and 38.8 ± 35.5% and 38.3 ± 33.0% (total JKOM score) for the low- and intermediate-molecular-weight HA groups, respectively. These results were not significantly different between the two groups ($p = 0.638$ and $p = 0.756$ for pain VAS and total JKOM score, respectively).

The rates of responder in the low- and intermediate-molecular-weight HA groups were 82.1% and 77.4%, respectively. These results were not significantly different between the two groups ($p = 0.752$).

Discussion

The present prospective study revealed that low- and intermediate-molecular-weight HA do not exhibit any significant difference in terms of efficacy such as pain VAS, JKOM score, and rate of responder as a first-line treatment for knee OA.

A previous study has reported that a weekly injection of low-molecular-weight HA for 5 weeks improved the clinical outcomes

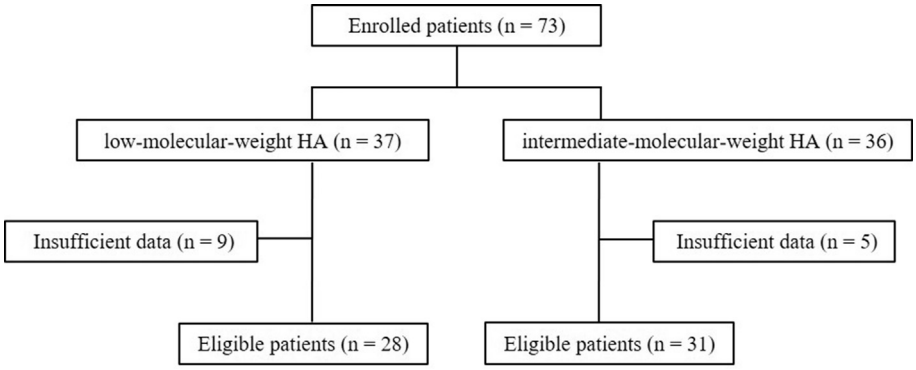

Fig. 1. Enrollment and outcomes.

Table 1
Demographic and clinical characteristics of the study population at baseline.

Variable	All patients (n = 59)<	Low group (n = 28)<	Intermediate group (n = 31)<	*p* value
Age, years				0.138
Mean (SD)	67.0 (9.1)	69.0 (7.9)	65.2 (9.8)	
Median (IQR)	69 (61, 74)	72 (63, 75.75)	64 (57, 73)	
Sex, female, n (%)	41 (69.5)	19 (67.9)	22 (71.0)	1.000
BMI				0.200
Mean (SD)	23.8 (3.3)	23.1 (3.0)	24.5 (3.5)	
Median (IQR)	23.5 (21.6, 25.3)	23 (21, 25.9)	23.9 (22.0, 25.1)	
K/L grade, 1/2/3/4, n	8/21/26/4	3/9/14/2	5/12/12/2	0.869
Pain VAS				0.638
Mean (SD)	53.1 (23.3)	48.4 (20.3)	57.2 (25.3)	
Median (IQR)	49 (35, 77)	44 (30.5, 63.25)	56 (35, 79)	
JKOM score: total				0.179
Mean (SD)	32.4 (18.6)	30.1 (19.3)	34.5 (17.9)	
Median (IQR)	27 (19, 42)	25 (17, 38.75)	29 (20, 46)	
JKOM score: pain and stiffness				0.162
Mean (SD)	12.0 (6.3)	10.9 (6.3)	13.0 (6.2)	
Median (IQR)	10 (7, 15)	8.5 (7, 14.75)	12 (7, 18)	
JKOM score: activities of daily living				0.518
Mean (SD)	10.2 (8.0)	9.5 (7.7)	10.7 (8.3)	
Median (IQR)	8 (5, 15)	6 (4.25, 12.75)	8 (5, 16)	
JKOM score: social activities				0.334
Mean (SD)	6.7 (4.6)	6.3 (5.2)	7.0 (4.2)	
Median (IQR)	6 (3, 10)	5 (2, 9.5)	6 (3, 11)	
JKOM score: general health				0.185
Mean (SD)	3.6 (1.8)	3.3 (1.8)	3.8 (1.8)	
Median (IQR)	3 (2, 5)	3 (2, 4.75)	3 (3, 5)	

Definitions: Low group, patients who received low-molecular-weight hyaluronic acid; Intermediate group, patients who received intermediate-molecular-weight hyaluronic acid group; SD, standard deviation; IQR, inter quartile range; BMI, body mass index; K/L, Kellgren–Lawrence; VAS, visual analog scale; JKOM, Japanese Knee Osteoarthritis Measure.

in patients with knee OA with K/L grade II or III compared with saline control according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain and physical function.[18] Moreover, administration of intermediate-molecular-weight HA in the same regimen has been shown to significantly increase the JKOM score in patients with knee OA with K/L grade II or III.[17]

Previous in *vivo* studies have reported the efficacy of HA for cartilage protection and synovitis suppression in a sheep model of OA, with intermediate-molecular-weight HA reported to be more effective than low-molecular-weight HA.[19] In a rabbit model of OA, intermediate-molecular-weight HA was found to be more effective than low-molecular-weight HA for the inhibition of cartilage degeneration.[20] In a canine model of arthritis, pathological changes such as thickening of synovial lining layers, vacuolar alterations in lining cells, and stainability of HA in the synovium were more suppressed by low than intermediate-molecular-weight HA.[21] Although these studies provide useful preliminary information, the translation of these results to clinical evidence is unclear.

A previous clinical trial comparimg the effects of thrice weekly administration of low- (500–730 kD) and intermediate- (800–1500 kDa) molecular-weight HA in patients with knee OA (K/L grade II or III) found no difference in WOMAC pain score after 6 weeks.[22] In the present study, there was no significant difference in the scores of pain VAS and JKOM score of pain and stiffness at week 6. The patients of this study were included also K/L grade I. Serum HA reflects the status synovitis and radiographic severity in patients with knee OA.[23–25] Therefore, we believe that the patients with mild knee OA affected the results. Although high-molecular-weight HA was not included, in previous study, IA of high-molecular-weight HA reduced 29.9–35.5 in pain VAS.[26,27] In this study, pain VAS in the low- and intermediate-molecular-weight HA groups were reduced 25.5 and 27.1, respectively. In reduction of pain VAS, as previously reported, high-molecular-weight HA may more effective than low- and intermediate-molecular-weight HA. Of 188 patients, 7 experienced severe adverse events due to high-

Table 2
Clinical results at baseline and follow-up of the low- and intermediate-molecular-weight hyaluronic acid groups.

Variable	Baseline	Follow-up	*p* value
Low group, mean (SD)			
pain VAS	48.4 (20.3)	22.9 (19.7)	<0.001
JKOM score: total	30.1 (19.3)	16.1 (10.5)	<0.001
JKOM score: pain and stiffness	10.9 (6.3)	6.1 (3.1)	0.001
JKOM score: activities of daily living	9.5 (7.7)	4.3 (4.5)	0.001
JKOM score: social activities	6.3 (5.2)	3.6 (3.6)	0.008
JKOM score: general health	3.3 (1.8)	2.1 (1.9)	<0.001
Intermediate group, mean (SD)			
pain VAS	57.2 (25.3)	30.1 (23.5)	<0.001
JKOM score: total	34.5 (17.9)	20.1 (12.4)	<0.001
JKOM score: pain and stiffness	13.0 (6.2)	7.1 (4.6)	<0.001
JKOM score: activities of daily living	10.7 (8.3)	5.9 (5.0)	<0.001
JKOM score: social activities	7.0 (4.2)	4.1 (3.8)	<0.001
JKOM score: general health	3.8 (1.8)	3.0 (1.6)	0.016

Definitions: Low group, patients who received low-molecular-weight hyaluronic acid; Intermediate group, patients who received intermediate-molecular-weight hyaluronic acid group; SD, standard deviation; VAS, visual analog scale; JKOM, Japanese Knee Osteoarthritis Measure.

molecular-weight HA.[27] We assume that safety is as reported.

In contrast, intermediate-molecular-weight HA was superior to low-molecular-weight HA as reflected by WOMAC scores for pain, function, and stiffness after 6 months of treatment.[22] Another study supported these results, reporting no difference in WOMAC score as well as European Quality of Life questionnaire results following treatment with low- and intermediate-molecular-weight HA[28] The results of the present study are in agreement with these results; however, the JKOM score includes aspects of Japanese lifestyle such as crouching and comforter tidying, which are not including in the WOMAC score. We believe that it is important for patient-reported outcomes to be adapted to the patients' country or culture. The general health score was significantly difference between the two groups. The general health score reflects health condition. Considering that there was no difference in pain or activities, the difference of general health may be related to comorbidities that had not been examined in this study.

The present study has some limitations that should be acknowledged. First, the sample size was small. However, we believe that this study provides important insights as a pilot study. Second, this study did not have a control group. A future study is required to clarify the effects of IA- low- and intermediate-molecular-weight HA including large sample size and control group.

In conclusion, both low- and intermediate-molecular-weight HA are effective in first-line treatment for patients with knee OA with significant clinical efficacy, as indicated by pain VAS and patient-reported outcomes. However, there is no difference in efficacy between the two, as indicated by the JKOM score. We believe that the results of this study provide important insights into the clinical management of Japanese patients with knee OA in daily practice.

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No founding was received for this study.

Declaration of competing interest

T. Mochizuki received honorariums for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Mochida, Pfizer, Tanabe-Mitsubishi, and Takeda. K. Yano received honorariums for lectures from AbbVie, Astellas, Ayumi, Bristol-Meyers, Eisai, Hisamitsu, Mochida, and Takeda. K. Ikari received honorariums for lectures from AbbVie, Astellas, Bristol-Myers, Chugai, Eisai, Eli Lilly, Janssen, Takeda, Tanabe-Mitsubishi, and UCB. The other authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asmart.2020.04.001.

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