


Original article

Sustained-release diclofenac conjugated to hyaluronate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 2 study

Yoshihiro Nishida ¹, Kazuyuki Kano², Yuji Nobuoka² and Takayuki Seo²

Abstract

Objective. To evaluate the efficacy and safety of diclofenac etalhyaluronate (DF-HA) (ONO-5704/SI-613), a novel DF-conjugated hyaluronate, in patients with knee OA in Japan.

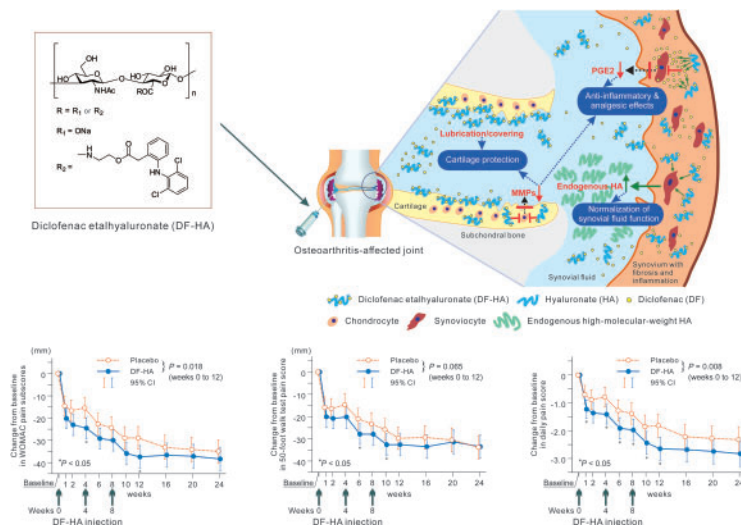
Methods. In this randomized, double-blind, placebo-controlled phase 2 study, patients were randomly assigned (1:1) to receive either 30 mg of DF-HA or placebo intra-articularly at weeks 0, 4 and 8 and were followed up for 24 weeks. The primary outcomes were changes from baseline in the WOMAC pain subscores, 50-foot walk test pain score and daily pain score. The secondary outcomes were the WOMAC physical function subscores, patient global assessment, responder rate and safety outcome.

Results. Overall, 176 patients received the investigational drugs (87 received DF-HA and 89 received placebo). The mean changes in the WOMAC pain subscores and daily pain score from baseline over 12 weeks after the first injection were significantly higher in the DF-HA than placebo group; the mean difference was -7.0 mm [95% CI, -12.7 , -1.2 ; $P = 0.018$] and -0.61 (95% CI, -1.06 , -0.16 ; $P = 0.008$), respectively. The difference in the 50-foot walk test pain score was -5.0 mm (95% CI, -10.3 , 0.3 ; $P = 0.065$). Improvement of pain by DF-HA was observed at week 1 and maintained from week 12 to week 24. Significantly greater improvements in the secondary outcomes were also observed with DF-HA than with placebo. No clinically significant adverse events occurred.

Conclusion. DF-HA reduced pain in patients with knee OA without major safety concerns.

Trial registration. UMIN Clinical Trials Registry, <https://www.umin.ac.jp/ctr/index.htm>, UMIN000015858

Key words: OA, diclofenac, hyaluronan, intra-articular injection, sustained-release, diclofenac etalhyaluronate, NSAIDs, knee, ONO-5704/SI-613, SI-613



¹Department of Rehabilitation, Orthopaedic Surgery, Nagoya University Hospital, Nagoya and ²Research & Development Division, Clinical Development Department, Seikagaku Corporation, Tokyo, Japan

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Correspondence to: Yoshihiro Nishida, Department of Rehabilitation, Orthopaedic Surgery, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8560, Japan.
E-mail: ynishida@med.nagoya-u.ac.jp

Rheumatology key messages

- Diclofenac etalhyaluronate is a new medication for IA injection in patients with knee OA.
- Repeated doses of diclofenac etalhyaluronate improve symptoms of knee OA without clinically problematic adverse effects.
- Improvement in patients with knee OA was observed at week 1 and maintained from week 12 to week 24.

Introduction

Knee OA is the most common chronic and progressive joint disorder associated with ageing and is a leading cause of disability in advanced-age people [1–3]. Worldwide, ~250 million people have OA, including OA of the knee [2, 3]. Major problems associated with OA are pain and loss of joint function caused by degeneration and destruction of the joint structure, including the articular cartilage, which leads to impaired health-related quality of life and activities of daily living [2–4]. Management of knee OA before surgery includes non-pharmacological and pharmacological therapies. Non-pharmacological therapies such as education, exercise programmes, taping and dietary weight management are recommended and used alone or along with pharmacological therapies [1, 5]. Pharmacological approaches to relieve pain and improve function in patients with knee OA commonly involve oral or topical administration of NSAIDs or selective cyclooxygenase-2 inhibitors as well as IA injection of CS (generally glucocorticoids) and HA [1, 3, 4, 6]. Although various pharmacological and non-pharmacological therapies including physical therapy exist for knee OA, their expected strength or onset of efficacy are different [1, 3, 5]. Recently, a randomized clinical trial demonstrated that patients with knee OA who underwent physical therapy had less pain and functional disability at 1 year than those who received IA glucocorticoid injection [7, 8]. In addition, because patient characteristics and complications need to be considered, it is recommended that an appropriate therapy be selected by relevant medical providers in accordance with the patient's medical status and/or preferences [1, 3, 5].

Diclofenac etalhyaluronate (DF-HA) (ONO-5704/SI-613) is a novel HA derivative (600 000–1 200 000 Da) in which the DF molecule is attached via a 2-aminoethanol linker to the glucuronic acid moiety of HA. It was developed as an IA injectable drug for the treatment of OA (Fig. 1A). DF-HA releases DF through hydrolytic cleavage of the ester linkage [9]. The putative mechanism behind the effect of DF-HA on knee OA is shown in Fig. 1B. DF-HA is expected to exhibit anti-inflammatory and analgesic effects, protect cartilage and normalize SF function in OA-affected joints based on the following multiple mechanisms. Once DF-HA is injected into the articular cavity of a knee joint with OA, it gradually releases DF in a sustained manner [9]. The released DF

inhibits the synthesis of prostaglandin E₂, a key mediator of inflammation and pain [9]. Similar to HA, DF-HA inhibits the production of MMPs in chondrocytes (unpublished observation), which are involved in inflammation and cartilage degradation [10–13]. DF-HA functions as a lubricant and shock absorber on the surface of cartilage in a manner similar to that of HA and protects cartilage from degeneration [6, 14]. In addition, DF-HA induces the production of endogenous high-molecular-weight HA in synoviocytes in contrast to DF or HA by enhancing the messenger ribonucleic acid (mRNA) expression of HA synthase 2 [15], which synthesizes long-chain HA (molecular weight of ≥ 3900 kDa) [16], and by suppressing the mRNA expression of hyaluronidase 2, which degrades HA [15]. IA injection of DF-HA is expected to relieve pain and improve joint function in patients with knee OA.

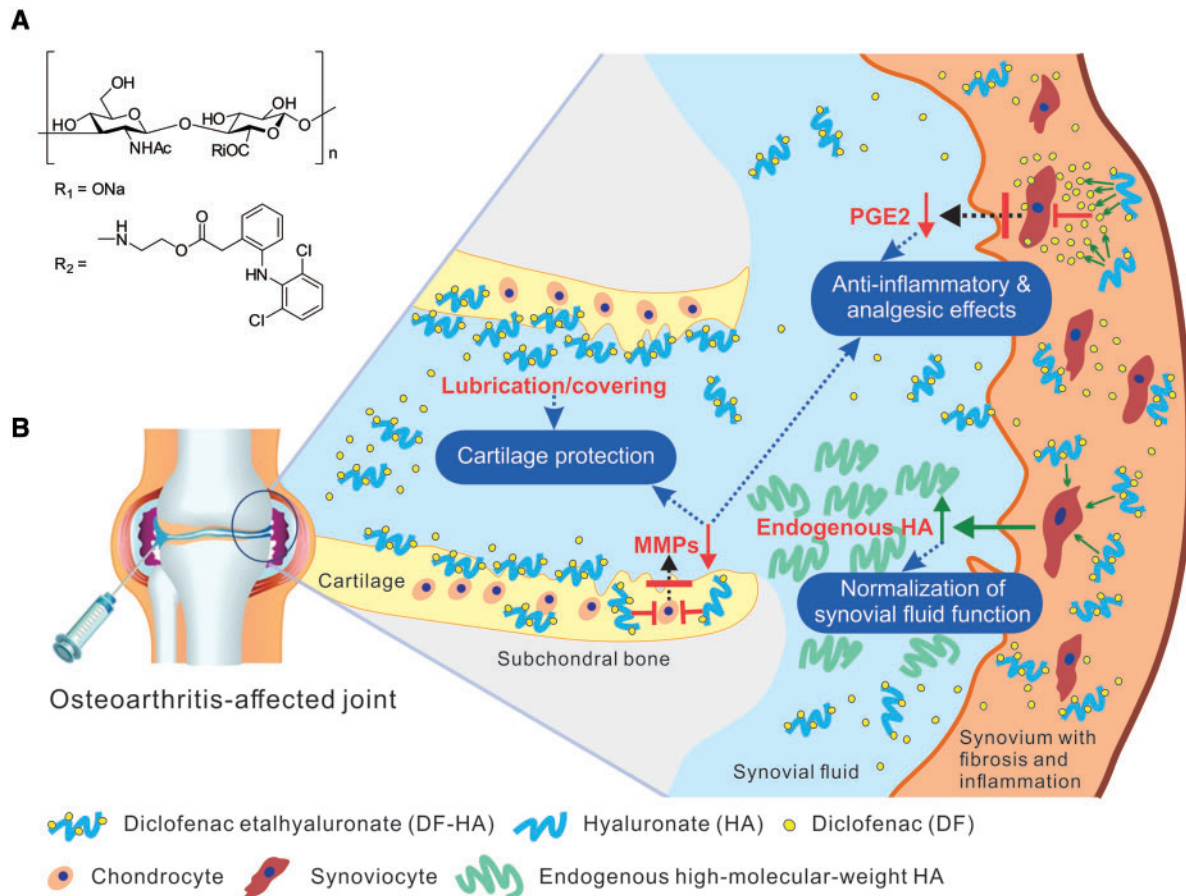
A previous exploratory study of a single IA injection of DF-HA involving 121 patients (UMIN000010167) provided preliminary evidence of the safety and efficacy of 30 mg of DF-HA in patients with knee OA (unpublished observation). Therefore, we conducted a randomized, double-blind, placebo-controlled phase 2 study (UMIN000015858) to evaluate the safety and efficacy of multiple IA injections of 30 mg of DF-HA (three times over 4 weeks) in patients with knee OA.

Methods

Study design and patients

This multicentre, randomized, placebo-controlled, double-blind, parallel-group comparison phase 2 study was performed to evaluate the efficacy and safety of multiple IA injections of DF-HA (Seikagaku Corporation, Tokyo, Japan) in patients with knee OA at 18 sites in Japan. The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice Guideline and in conformity with the Declaration of Helsinki. The institutional review board of each participating centre approved the study, and all patients provided written informed consent.

At the time of screening, eligible patients were 40–75 years of age and had a diagnosis of knee OA according to the ACR [17], a ≥ 12 -week history of pain, a Kellgren–Lawrence radiographic score of 2 or 3 at the target knee [18], a mean WOMAC pain subscore of 50–90 mm (inclusive) at the target knee, and a mean visual

Fig. 1 Chemical structure and mechanism of action of diclofenac etalhyaluronate

(A) Chemical structure of N-[2-[[2-[[2-(2,6-dichlorophenyl)amino]phenyl]acetyl]oxy]ethyl] hyaluronamide (diclofenac etalhyaluronate, ONO-5704/SI-613). (B) The envisioned mechanism of action of DF-HA. DF-HA: diclofenac etalhyaluronate; PGE2: prostaglandin E2.

analogue scale (VAS) score of ≤ 30 mm at the contralateral knee (100-mm VAS) [19]. Additionally, the 50-foot walk test pain score [20] was added to the eligibility criteria in the middle of the study because some patients had imbalanced pain ratings involving a low score for the 50-foot walk test but a high WOMAC pain subscore. The exclusion criteria were secondary OA, other diseases involving pain in the lower extremity, a surgical or invasive procedure involving the lower extremity, or a BMI of ≥ 35.0 kg/m².

Randomization and blinding

Patients were randomly allocated in a 1:1 ratio to either the DF-HA or placebo group by a minimization method using an interactive Web response system [21], according to a random allocation sequence generated by an independent assignment manager in the Web response centre. Patients were stratified within each site according to a Kellgren–Lawrence score of 2 or 3, a mean VAS score of < 70 or ≥ 70 mm for five items of the baseline WOMAC pain subscale, and a baseline VAS score of < 70 or

≥ 70 mm for the 50-foot walk pain test. The study was conducted in a double-blind manner. The appearance, preparation method and injection procedure, but not the viscosity, were identical between DF-HA and placebo. Therefore, the physician who injected the investigational drugs and the investigator who assessed the outcomes were separated, and the former was not allowed to evaluate the efficacy and safety. Except for the investigator who injected the investigational drugs, all patients, investigators, and other stakeholders were blinded to treatment allocation until database closure.

Intervention

Patients were screened between 1 week before randomization and the day of randomization. All patients received an IA injection of either the DF-HA (prefilled syringe containing 30 mg per 3 ml of DF-HA; Seikagaku Corporation) or the placebo drug (prefilled syringe containing 3 ml of citric acid–sodium citrate buffered solution; Seikagaku Corporation) at weeks 0, 4 and 8. The

patients were followed up for 24 weeks after the first injection (at weeks 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24).

The patients were prohibited from using analgesic medications, including NSAIDs, CS, opioids or psychotherapeutic drugs that affect the assessment of disease-associated pain, throughout the study period after providing informed consent. The use of acetaminophen as a rescue medication for pain relief in the target knee was permitted, but its use was prohibited from 2 days prior to each visit, including screening. Patients receiving regular physical therapy for the target knee before the start of screening were allowed to continue this therapy during the study if the frequency and intensity were not increased. The patients were instructed not to change the intensity or frequency of exercise performed in their daily activities.

Outcomes

The primary outcomes were changes from baseline in the WOMAC pain subscores on a 100-mm VAS, 50-foot walk test pain scores on a 100-mm VAS, and daily pain score on an 11-point numerical rating scale according to the patients' diaries. The WOMAC pain subscores and 50-foot walk test pain score were assessed at each visit, and the diary was filled out by the patient every day. The data at each time point were the mean values from the last visit to the day before the time point.

The secondary outcomes were the changes from baseline in the WOMAC (stiffness subscores, physical function subscores and total scores on a 100-mm VAS), responder rate/strict responder rate according to the OMERACT and Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria [22], scores for the patient/physician global assessment and Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Japanese standard version 2 [23–25], and consumption of acetaminophen provided as a rescue medication.

The safety outcomes were treatment-emergent adverse events (TEAEs), treatment-related TEAEs and serious TEAEs. These were defined as any investigator-assessed unfavourable or unintended sign, symptom or disease that occurred after the first injection, including abnormal clinical laboratory test results, vital signs and target knee examination findings (joint effusion, swelling and redness).

Statistical analysis

The results of a previous study (UMIN000010167) in which 121 patients with knee OA were randomly allocated into three groups to receive a single IA injection of 15 mg of DF-HA ($n = 40$), 30 mg of DF-HA ($n = 41$) or placebo ($n = 40$) suggested the efficacy of 30 mg of DF-HA (unpublished observation). In the present study, the sample size was set at 160 patients ($n = 80$ in each group) with consideration of feasibility and the results of the previous study.

Efficacy was evaluated in the full analysis set, which included patients who received at least one injection of

the investigational drug. The primary endpoints (least square mean changes in the primary outcomes from baseline over 12 weeks after the first injection) were compared between the two treatment groups using a mixed model for repeated measures at each time point from week 1 through 12. The model included the baseline scores, treatment, time point, treatment-by-time point interaction, and Kellgren–Lawrence grading score as fixed effects. An unstructured covariance was used to model the covariance structure among repeated measures. As a secondary analysis, the primary outcomes at each time point from week 1 through 24 were compared between the two treatment groups using the same model as for the primary analyses. The same analysis approach as used for the primary outcomes was repeated for the secondary outcomes of the WOMAC (stiffness subscores, physical function subscores and total scores), patient/physician global assessment scores, and three summary scores of the SF-36. The responder rate/strict responder rate according to the OMERACT-OARSI responder criteria were analysed using generalized estimating equations from week 1 to week 12 and from week 1 to week 24. The changes in the mean consumption of acetaminophen per day from baseline were summarized by treatment and time point using descriptive statistics. Two-sided P -values of <0.05 were considered to indicate statistical significance. Multiplicity was not considered to evaluate the effectiveness in an exploratory manner.

Safety was evaluated in the safety set, which included patients who received the treatment at least once. All reported TEAEs were coded using the Medical Dictionary for Regulatory Activities v.18.1; other safety outcomes were summarized by treatment group. All statistical analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC, USA).

Results

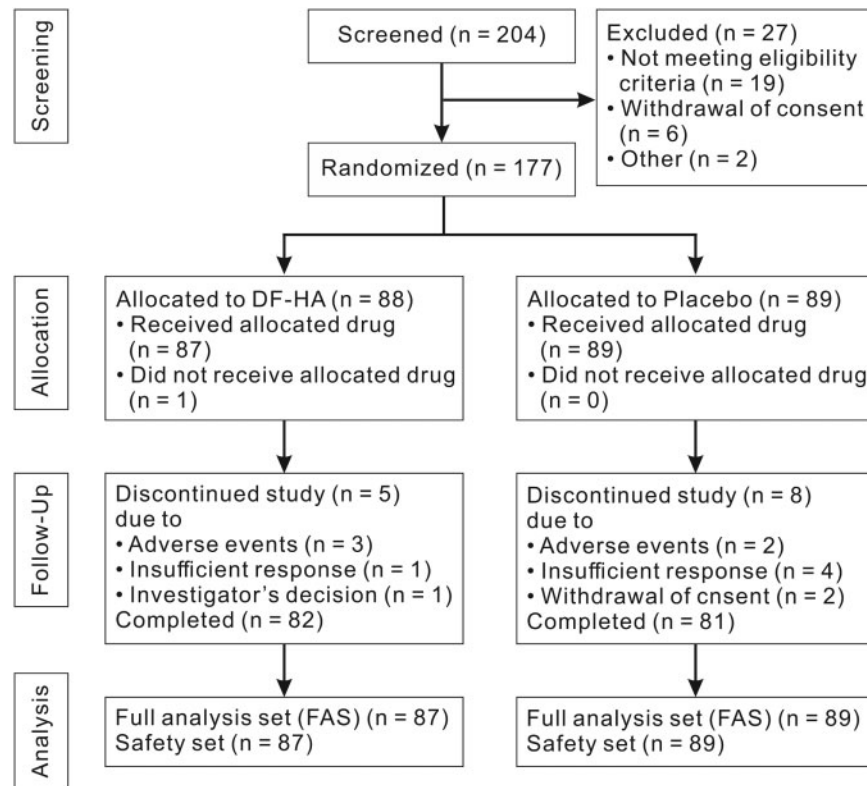
Patients

From December 2014 to July 2015, 204 patients were screened for eligibility, and 177 patients were enrolled and randomly assigned to the DF-HA group ($n = 88$) or the placebo group ($n = 89$). One patient in the DF-HA group was withdrawn from the study before treatment. Thus, the full analysis set and safety set included 176 patients (DF-HA, $n = 87$; placebo, $n = 89$). Of these 176 patients, 13 withdrew from the study after the first injection (DF-HA, $n = 5$; placebo, $n = 8$) and 163 completed the study (DF-HA, $n = 82$; placebo, $n = 81$) by the end of follow-up in December 2015 (Fig. 2). The patients' baseline characteristics were balanced between the two groups (Table 1).

Efficacy

All primary analyses for the primary outcomes indicated the efficacy of DF-HA for pain relief over 12 weeks. Changes over 12 weeks from baseline in the WOMAC

Fig. 2 Patient disposition



DF-HA: diclofenac etalhyaluronate.

pain subscores, 50-foot walk test pain score and daily pain score were significant in both the DF-HA and placebo groups, and these changes were greater in the DF-HA than placebo group; these differences were -7.0 mm [95% CI, -12.7 , -1.2 ; $P = 0.018$], -5.0 mm (95% CI, -10.3 , 0.3 ; $P = 0.065$), and -0.61 (95% CI, -1.06 , -0.16 ; $P = 0.008$), respectively (Fig. 3A–C). Additionally, these three primary outcome scores improved after every injection, and a trend towards superior mitigation of pain was observed as early as 1 week after the initial treatment in the DF-HA group compared with the placebo group. Although there were no significant differences in these pain scores between the two groups after 12 weeks, their improvement values from baseline were maintained without worsening in the DF-HA group after week 12 to week 24 (Fig. 3D–F, Supplementary Table S1, available at *Rheumatology* online).

Before adding the criterion of the 50-foot walk test pain score to the eligibility criteria in the middle of the study, 87 patients were enrolled (DF-HA, $n = 45$; placebo, $n = 42$), and 90 patients were enrolled thereafter (DF-HA, $n = 43$; placebo, $n = 47$), including one patient who was withdrawn before treatment in the DF-HA group. There was greater improvement in the three primary outcomes in the DF-HA than placebo group both before and after protocol amendment, although the difference in

improvement between the DF-HA and placebo groups was greater after protocol amendment (Supplementary Table S2, available at *Rheumatology* online).

The mean changes in the secondary outcomes (WOMAC physical function subscores, WOMAC total scores, and patient/physician global assessment scores) from baseline were significantly higher in the DF-HA than placebo group (Table 2).

The OMERACT-OARSI responder rate at each time point was greater in the DF-HA than the placebo group, and the responder rate at week 12 was 81.0% and 69.1%, respectively. The mean odds ratio over 12 weeks was 2.04 (95% CI, 1.2, 3.3; $P = 0.005$). Similar results were observed in the strict responders over 12 weeks, with an odds ratio of 1.97 (95% CI, 1.2, 3.3; $P = 0.010$). The change from baseline in mean daily acetaminophen consumption at each time point decreased to a greater extent in the DF-HA than placebo group. The detailed results of the secondary outcomes at each time point are shown in Supplementary Tables S1, S3 and S4, available at *Rheumatology* online.

Safety

All TEAEs were experienced by 50 of 87 patients (57.5%) injected with DF-HA and by 52 of 89 patients (58.4%) injected with placebo; there was no significant difference in the incidence between the treatment

TABLE 1 Patients' demographic and baseline characteristics

Variables	DF-HA	Placebo
	n=87	n=89
Age, years	63.2 ± 8.6	65.3 ± 8.1
Male	26 (29.9)	21 (23.6)
Female	61 (70.1)	68 (76.4)
BMI, kg/cm ²	25.58 ± 3.28	24.81 ± 3.68
Duration of current pain, weeks	164.0 ± 212.2	185.9 ± 225.1
Kellgren–Lawrence grade		
Grade 2	58 (66.7)	61 (68.5)
Grade 3	29 (33.3)	28 (31.5)
WOMAC pain subscores, mm	65.9 ± 8.0	66.4 ± 8.0
<70	59 (67.8)	59 (66.3)
≥70	28 (32.2)	30 (33.7)
WOMAC stiffness subscores, mm	53.4 ± 22.0	54.0 ± 20.7
WOMAC physical function subscores, mm	57.0 ± 17.0	57.3 ± 15.5
WOMAC total scores, mm	58.5 ± 14.4	58.9 ± 13.1
50-foot walk test pain score, mm	60.3 ± 15.5	60.8 ± 14.4
<50	11 (12.6)	11 (12.4)
≥50 to <70	56 (64.4)	57 (64.0)
≥70	20 (23.0)	21 (23.6)
Daily pain score	6.7 ± 1.3	6.5 ± 1.1
Patient global assessment, mm	67.2 ± 15.2	65.0 ± 14.9
Physician global assessment, mm	63.3 ± 11.8	63.2 ± 11.9
SF-36 summary score		
MCS	54.0 ± 7.9	56.1 ± 9.2
RCS	45.7 ± 13.6	45.0 ± 13.4
PCS	28.9 ± 11.4	28.0 ± 9.9
Daily acetaminophen consumption, mg/day	182.2 ± 371.9	142.3 ± 333.0

Data are presented as mean ± s.d. or *n* (%).

DF-HA: diclofenac etalhyaluronate; MCS: mental component summary; PCS: physical component summary; RCS: role/social component summary; SF-36: Medical Outcomes Study 36-Item Short Form Health Survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index version 3.1.

groups (Table 3). No deaths occurred, and serious TEAEs were reported by one patient injected with DF-HA and two patients injected with placebo. These serious TEAEs were judged by the investigators to be unrelated to the treatment. A cardiac disorder (reported as 'heart disease suspect') occurred in one patient treated with DF-HA, but no abnormality in cardiac function was detected by a subsequent catheter examination. Pneumonia (reported as 'acute pneumonia') and breast cancer (reported as 'left breast cancer suspect') were observed in the placebo group. The pneumonia resolved with inpatient treatment. The breast cancer did not resolve, and the patient underwent surgery after the study. The TEAE leading to discontinuation of the repeat-dosing study treatment was injection site joint inflammation in one patient injected with DF-HA. This event was mild and judged by the investigator to be treatment-related, and it resolved 15 days after onset without therapy. No other treatment-related TEAEs were reported. TEAEs were experienced by ≥3% of patients in each group, and their incidences are shown in Table 3.

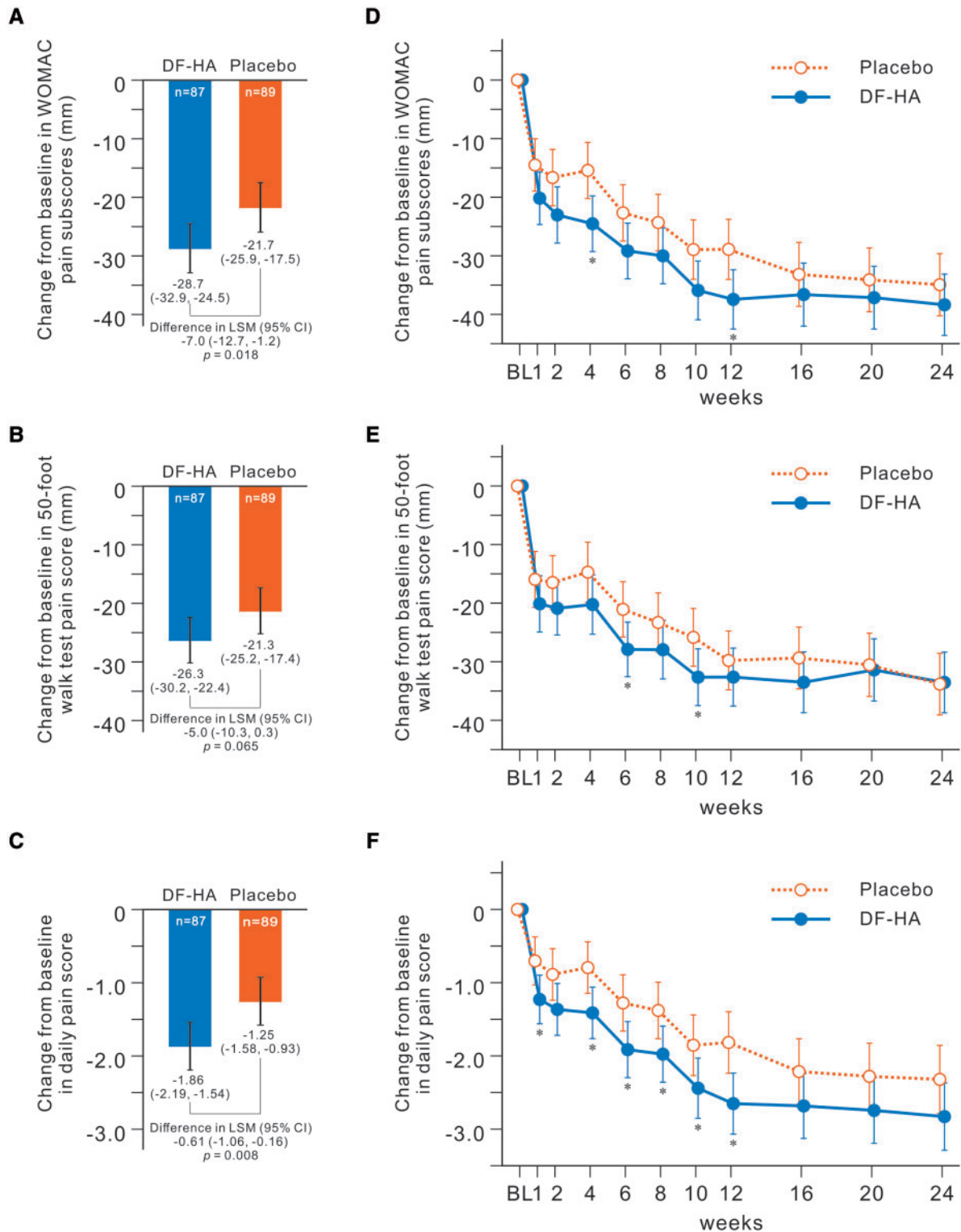
No clinically significant changes were reported in the clinical laboratory tests, vital signs or target knee examination tests.

Discussion

This clinical study is the first to report the efficacy and safety of multiple IA injections of DF-HA in patients with knee OA. Injection of DF-HA showed superior efficacy compared with placebo for relieving pain as indicated by primary outcome following three monthly treatments. The study included three primary outcome measures of pain severity: the WOMAC pain subscores, the 50-foot walk test pain score and the daily pain score derived from the patients' diaries. The WOMAC pain subscores, daily pain score and 50-foot walk test pain score were significantly decreased from baseline after the first injection in the placebo group as well as the DF-HA group. These decreases were thought to be placebo effects, because IA injection itself was reported to have a large placebo effect [26, 27]. The WOMAC pain subscores and daily pain score indicated that pain mitigation was significantly superior in the DF-HA group, and the 50-foot walk test pain score indicated a trend towards superior pain mitigation over 12 weeks after the first injection.

In this clinical study, a single IA injection of DF-HA showed significant early-onset efficacy and a long-

Fig. 3 Primary outcomes



Least square means of changes from baseline over 12 weeks and treatment differences in the (A) WOMAC pain subscores, (B) 50-foot walk test pain score and (C) daily pain score between the two study groups as analysed by a mixed model for repeated measures. Time series of change from baseline at weeks 1 to 24 for (D) WOMAC pain subscores, (E) 50-foot walk test pain score and (F) daily pain score between the two study groups. * $P < 0.05$ (significantly different from placebo). Error bars: 95% CI. BL: baseline.

TABLE 2 Summary of analysis for secondary outcomes over 12 weeks

	LSM change (95% CI)		LSM difference (95% CI)	P-value
	DF-HA n = 87	Placebo n = 89		
WOMAC score				
WOMAC stiffness subscores	−18.5 (−22.6, −14.4)	−13.1 (−17.3, −9.0)	−5.4 (−11.0, 0.2)	0.061
WOMAC physical function subscores	−20.8 (−24.6, −16.9)	−14.1 (−18.0, −10.2)	−6.7 (−12.0, −1.4)	0.014
WOMAC total scores	−22.3 (−26.1, −18.5)	−15.7 (−19.6, −11.9)	−6.6 (−11.9, −1.4)	0.014
Patient global assessment	−24.0 (−27.7, −20.3)	−16.4 (−20.1, −12.7)	−7.6 (−12.7, −2.5)	0.004
Physician global assessment	−21.5 (−24.7, −18.4)	−16.5 (−19.7, −13.3)	−5.1 (−9.4, −0.7)	0.023
SF-36 summary score				
MCS	0.2 (−0.9, 1.3)	0.7 (−0.4, 1.8)	−0.5 (−2.0, 1.1)	0.538
RCS	1.8 (−0.1, 3.6)	0.3 (−1.6, 2.2)	1.5 (−1.1, 4.0)	0.253
PCS	6.3 (4.6, 8.0)	4.0 (2.2, 5.7)	2.3 (0.0, 4.6)	0.054

The LSM change in the secondary outcomes from baseline over 12 weeks were compared between the DF-HA and placebo groups based on the mixed model for repeated measures at each time point from week 1 through 12.

DF-HA: diclofenac etalhyaluronate; LSM: least square mean; MCS: mental component summary; PCS: physical component summary; RCS: role/social component summary; SF-36: Medical Outcomes Study 36-Item Short Form Health Survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index version 3.1.

TABLE 3 Summary of TEAEs

	DF-HA (n = 87)	Placebo (n = 89)
Patients with at least one TEAE	50 (57.5)	52 (58.4)
Patients with serious TEAEs	1 (1.1)	2 (2.2)
Cardiac disorder	1 (1.1)	0 (0.0)
Breast cancer	0 (0.0)	1 (1.1)
Pneumonia	0 (0.0)	1 (1.1)
Patients with TEAEs leading to investigational drug withdrawal	1 (1.1)	0 (0.0)
Injection site joint inflammation ^a	1 (1.1)	0 (0.0)
Any TEAEs in ≥3% of patients		
Nasopharyngitis	21 (24.1)	13 (14.6)
Osteoarthritis	5 (5.7)	5 (5.6)
Periodontitis	3 (3.4)	0 (0.0)
Contusion	3 (3.4)	3 (3.4)
Back pain	0 (0.0)	3 (3.4)
Increased blood creatine phosphokinase level	0 (0.0)	3 (3.4)

Data are presented as n (%).

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities, version 18.1.

^aTreatment-related TEAE was injection site joint inflammation only.

DF-HA: diclofenac etalhyaluronate; TEAEs: treatment-emergent adverse events.

lasting analgesic effect for 4 weeks comparable to that reported in animal models of OA [9]. Significant improvement in the DF-HA group was observed at 1 week after the first injection. The onset of the effect of DF-HA seems to be much faster than that of unconjugated HA (5–13 weeks after injection) [28]. Furthermore, a trend towards superior improvement of pain by DF-HA was maintained from week 12 to week 24 following three

monthly injections. Additionally, DF-HA showed a trend towards improved knee OA symptoms, including stiffness, physical function and pain. We speculate that the outcomes of this study resulted from the envisioned multiple mechanisms of action of DF-HA, which has the advantages of both DF and HA (i.e. anti-inflammatory and analgesic effects, cartilage protection, and normalization of SF function) [9, 11].

The major complaints reported by patients with knee OA are joint pain and limitation of function, which result in considerable morbidity, impairment of quality of life, and social and economic burdens. The OARSI has recommended a core set of three measures for clinical trials involving patients with knee OA: pain, physical function and patient global assessment [29]. The treatment with DF-HA in the present study significantly improved these core measures. To evaluate the clinical efficacy of a new treatment, it is necessary to show not only the statistical significance of its effectiveness over the comparative treatment but also the clinical significance of its effectiveness (the size of the treatment effect). For this purpose, the minimal clinically important improvement (MCII) should be considered [30]. The previously reported MCII were −19.9 mm for pain intensity, −9.1 for WOMAC physical function subscores and −18.3 mm for patient global assessment [30]. The changes in all three measurements in the present study were higher than these previously reported MCII scores. These results show the potential of DF-HA as a clinically useful drug to improve the core symptoms of knee OA.

Oral and topical NSAIDs are widely used, and their safety has been well documented [31–34]. However, because IA injection of NSAIDs is not approved, IA safety profiles of NSAIDs have not been established. Although one treatment-related adverse reaction (injection site joint inflammation) occurred in the present study, it was

not a significant TEAE of DF-HA as judged by the symptoms and lack of requirement for therapy. Overall, no major safety concerns emerged in this study.

Administration of sustained-release anti-inflammatory and/or analgesic drugs into a target joint of patients with OA is expected to minimize the toxic effects and maximize the local efficacy of these drugs [35–40]. Although the results of this study should be interpreted with care, DF-HA appears to be a promising candidate with such properties. However, this study may have some limitations associated with the lack of an active comparator arm and relatively high placebo effects, which made it difficult to assess the magnitude of the treatment effect. Therefore, additional studies involving higher numbers of patients, a longer duration of administration, active comparator arms including not only pharmaceutical but also non-pharmaceutical therapies such as physical therapy, and combination treatment with them are required to confirm our present findings and show that the safety and efficacy of DF-HA justifies its use in general practice.

In conclusion, these study findings suggest that DF-HA, with the advantages of DF and HA, is a novel potent treatment for knee OA that improves symptoms in patients without major safety concerns. These results support the performance of a validation phase 3 study with higher numbers of patients.

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employees of Seikagaku Corporation. The other authors have declared no conflicts of interest.

Data sharing: The data that support the findings of this study are available upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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