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Nonanimal Hyaluronic Acid for the Treatment of Ankle Osteoarthritis: A Prospective, Single-Arm Cohort Study

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ABSTRACT

Ankle osteoarthritis (OA) can cause disabling symptoms, and some patients prefer to be treated with minimally invasive procedures. Nonanimal hyaluronic acid (NASHA) is a cross-linked hyaluronic acid product that has a prolonged intra-articular residence time. The authors report the first study of NASHA for the treatment of ankle OA. Thirty-seven patients with Kellgren-Lawrence grade II or III ankle OA received an intra-articular injection of NASHA (1 mL). Outcomes included visual analogue scale (VAS) scores for pain and disability. At baseline, the mean VAS pain score was 50.1 ± 14.5 mm. During the 26-week follow-up period, the least squares (LS) mean change from baseline in the ankle OA VAS pain score was −20.5 mm (95% confidence interval [CI] −25.5 to −15.6 mm), an LS mean percentage reduction of 40.0% (95% CI 30.2% to 49.9%). The LS mean change from baseline in the VAS disability score during 26 weeks was −19.2 mm (95% CI −24.8 to −13.6 mm), a percentage reduction of 34% (95% CI 22.3% to 45.7%). Five participants experienced a total of 7 adverse events considered to be related to study treatment (injection site pain, n = 3; injection site joint pain, n = 3; plantar fasciitis, n = 1). This study shows promise for viscosupplementation with NASHA in the treatment of ankle OA. A single injection was associated with clinically meaningful reductions in pain and disability during a 26-week period and, in general, was well tolerated.

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Osteoarthritis (OA) is a common condition that has major impact on mobility and quality of life. OA of the ankle affects about 1% to 3% of the world's adult population (1–3). Although it is less common than OA of the hip or knee (4), OA of the ankle can be equally disabling, and it affects individuals at a younger age (5). Unlike knee and hip OA, only a minority of ankle OA cases are primary; most cases are attributable to trauma (6).

Surgical treatment options for ankle OA include ankle arthrodesis, arthrodiastasis, and total ankle replacement (7). These procedures involve a risk for complications, a recovery period, and repeat surgery (8,9). Nonoperative, joint-sparing treatment should always be tried first, particularly in younger patients, to delay the need for surgery. Such nonoperative treatment is required in patients whose symptoms are not severe enough to merit surgery (10). Other patients may wish to delay surgery for various reasons, such as the financial impact of recovery time.

Noninvasive treatment options include nonsteroidal antiinflammatory drugs, physiotherapy, and bracing. The effects of these

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interventions vary among patients. Although hyaluronic acid (HA) has not been shown to be superior to other conservative therapies, clinical trials have indicated that an intra-articular injection of HA may be an effective treatment for ankle OA (11–14).

Nonanimal hyaluronic acid (NASHA) is a biocompatible HA product with a prolonged intra-articular residence time (15,16). Investigations of the use of intra-articular NASHA injections for knee and hip OA have shown a long duration of action and favorable tolerability (17–21). In addition, preliminary results of NASHA treatment for thumb OA appear promising (22). Although the ankle joint differs biomechanically from the joints of the knee, hip, and thumb (23), it is possible that an intra-articular injection of NASHA is beneficial for ankle OA.

The purpose of this single-arm cohort study was to determine the effect of a single intra-articular injection of NASHA in the treatment of ankle OA. Our hypothesis was that pain during the first 26 weeks post-treatment would be less than pain at baseline, as measured with the use of a visual analogue scale (VAS).

Patients and Methods

This prospective, single-arm, open-label study with a 6-month follow-up period was performed at a single study center. The study was designed by A.Y. (the principal investigator), A.H., T.W., M.P., K.W., and J.N., and the protocol was fully reviewed and approved by the University of British Columbia–Providence Health Care Research Ethics Board. The study was performed in accordance with good clinical practice and the Declaration of Helsinki. It is registered at ClinicalTrials.gov, identifier number NCT02627859. The first participant was enrolled on September 24, 2014, and the last participant completed the study on August 25, 2016.

Participants were recruited for the study via a newspaper advertisement and at clinics held at the study center. Individuals were included in the study if they were aged 19 to 85 years and had a body mass index (BMI) of ≤35 kg/m^2, a diagnosis of mild to moderate ankle OA (Kellgren-Lawrence grade II or III) (24), a VAS pain score of 30 to 90 mm for the study ankle (scale range 0 to 100 mm) (25), chronic pain in the study ankle lasting ≥6 months, and willingness to discontinue oral and topical analgesia except for rescue use of acetaminophen. Individuals were excluded if they had significant pain in other joints that required analgesic therapy, a major hindfoot deformity, substantial venous or lymphatic stasis in the legs, a tense effusion, major misalignment or instability of the study ankle, surgery in the study ankle within the past 12 months, oral corticosteroid treatment within the previous month, intra-articular or periarticular injection of corticosteroids in the study ankle within the past 3 months, or intra-articular HA injection in the study ankle within the past 9 months. Nonpharmacological treatment of ankle OA (eg, physiotherapy) was permissible throughout the study, provided that it had been initiated before screening and was not substantially changed (except for discontinuation) during the study. A.S.E.Y., M.P., K.W., and J.N. were responsible for the enrollment of patients as well as their respective follow-up visits.

After the baseline assessment, each participant received a single injection of NASHA (Durolane®; Bioventus LLC, Durham, NC; 20 mg/mL sodium hyaluronate in a prefilled 1-mL syringe) into the study ankle joint, with the optional use of an intra-articular or subcutaneous anesthetic agent and optional use of imaging. This treatment was administered by one of the treating physicians (A.H., M.P., K.W., and J.N.). Follow-up assessments were performed at 6, 12, 18, and 26 weeks posttreatment. Efficacy was assessed by the study participants by using the ankle OA VAS pain score and ankle OA VAS disability score of the Ankle Osteoarthritis Scale (AOS), a validated outcome measure for ankle OA (25). The pain score was derived from 9 items: at its worst, before getting up, walking barefoot, standing barefoot, walking wearing shoes, standing wearing shoes, walking wearing shoe inserts/braces, stand wearing shoe inserts/braces, and walking fast or running. A different group of 9 items were assessed for the disability score: walking around the house, walking outside on uneven ground, walking 4 blocks or more, climbing stairs, descending stairs, standing on tiptoes, getting out of a chair, climbing up or down curbs, and walking fast or running. All items were assessed by using a VAS with a range from 0 mm ("no pain or disability") to 100 mm ("worst imaginable pain or disability"). Pain and disability scores were calculated as the mean of the 9 composite items. Additional outcomes included patient global assessment VAS score (study participants responded to the question, "Considering all the ways the arthritis of your study ankle affects you, how are you doing today?" by using a scale ranging from 0 mm ["very poor"] to 100 mm ["excellent"]) (26) and use of rescue medication, which was recorded by participants in a diary. Adverse events (AEs) were recorded and reported by study coordinators throughout the study (participants were asked at each study visit after baseline assessment, "Since your last clinical visit, have you had any health problems?"). The primary efficacy variable was change from baseline in ankle OA VAS pain score during the first 26 weeks post-treatment.

Statistical Analysis and Sample Size Calculation

The primary efficacy variable was analyzed by using mixed-effects repeated-measures regression, with baseline ankle OA VAS pain score and visit week as fixed-effects covariates. The criterion for study success was least squares (LS) mean reduction from baseline in VAS pain score during 26 weeks of at least 25%, and statistical significance was defined at the 5% ($p \leq .05$) level. The "during 26 weeks" estimate was based on data from all time-points (baseline and weeks 6, 12, 18, and 26), with the overall effect size reflecting the entire time period. All estimates of treatment effect during the study period were presented as LS mean values and percentage changes, with 95% confidence intervals (CIs). Efficacy data for each time-point were analyzed by using descriptive statistics (mean and standard deviation). Z.W. worked with A.H. to analyze the data.

For the detection of a 25% change in VAS pain score with 80% power and a baseline mean of 60 mm, a sample size of 29 was required. Therefore, a minimum of 36 study participants were recruited to allow for a dropout rate up to 20%.

Efficacy was assessed in the full analysis set, defined as all participants receiving study treatment with at least 1 post-treatment efficacy assessment. Safety was assessed in the safety set: all participants receiving study treatment.

Results

Study Participants

Fifty-one individuals were screened, of whom 37 (72.55%) were enrolled in the study. Reasons for exclusion were Kellgren-Lawrence grade IV in the study ankle (n = 6; 11.77%), Kellgren-Lawrence grade <II in the study ankle (n = 2; 3.9%), subtalar OA (n = 1; 1.96%), talonavicular joint OA (n = 1; 1.96%), inability to tolerate acetaminophen (n = 1; 1.96%), epidural corticosteroid injections for leg pain (n = 1; 1.96%), body mass index (BMI) >35 kg/m^2 (n = 1; 1.96%), and nonattendance of clinic visit (n = 1; 1.96%). All 37 enrolled individuals received the complete 1-mL volume of study treatment agent and were included in the full analysis set and the safety set. Two (5.41%) individuals discontinued the study early: 1 (2.7%) withdrew consent and 1 (2.7%) was lost to follow-up for an unknown reason, thought to be at random.

The mean age of the individuals in the full analysis set was 60.9 (range 33 to 85) years, and 21 (56.8%) of the study participants were male (Table 1). The participants' mean BMI was 27.3 (range 20 to 35) kg/m^2; 16 (43%) participants were overweight (BMI 25.0 to 29.9 kg/m^2) and 10 (27%) were obese (BMI 30.0 to 35.0 kg/m^2). Most participants (n = 32; 86.5%) had Kellgren-Lawrence grade III OA in the study ankle. Eight (21.6%) study participants were receiving nonpharmacological treatment for ankle pain; this treatment included physiotherapy (n = 3; 8.1%), walking (n = 3; 8.1%), and exercise, golf, heat, and tension bandage (n = 1 participant each; 2.7%). All study participants experienced a washout period lasting at least 5 half-lives of their analgesic medication.

Primary Efficacy Analysis

The LS mean change from baseline in the ankle OA VAS pain score during 26 weeks was −20.5 mm (95% CI −25.5 to −15.6 mm), an LS mean reduction of 40.0% (95% CI 30.2% to 49.9%). Therefore, the primary

Table 1
Participants' demographics and baseline characteristics (full analysis set, N = 37)

Characteristic	Mean ± SD or n (%)
Age (y)	60.9 ± 11.7
Male sex	21 (56.8)
Body weight (kg)	81.3 ± 16.6
Body mass index (kg/m^2)	27.3 ± 4.1
Ankle OA VAS pain score: study ankle	50.1 ± 14.5
Kellgren-Lawrence radiographic grade	
II	5 (13.5)
III	32 (86.5)

Abbreviations: OA, osteoarthritis; SD, standard deviation; VAS, visual analogue scale.

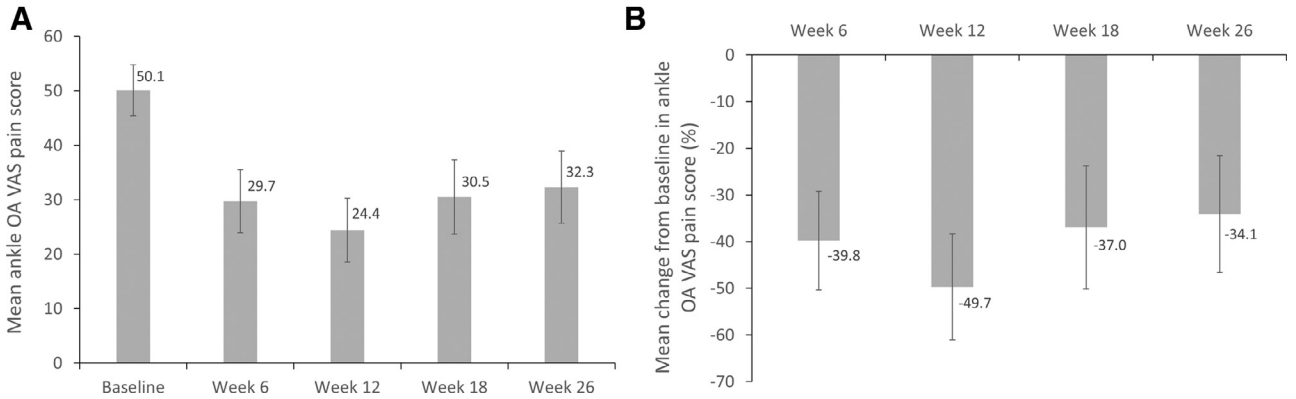

Fig. Primary efficacy analysis in the full analysis set (N = 37): (*A*) ankle osteoarthritis (OA) visual analogue scale (VAS) pain score and (*B*) percentage change from baseline in ankle OA VAS pain score. Error bars denote 95% confidence intervals.

Table 2
Secondary efficacy results in the full analysis set (N = 37)

Variable	Baseline	Week 6	Week 12	Week 18	Week 26
Ankle OA disability VAS score	51.5 ± 15.5	30.9 ± 20.8	27.3 ± 21.7	33.0 ± 22.7	37.1 ± 23.4
Patient global assessment VAS score	61.4 ± 22.8	71.1 ± 18.8	67.8 ± 23.4	62.2 ± 18.5	60.9 ± 23.0
Use of rescue medication since the previous clinic visit					
Participants, n/N (%)	1/6 (16.7)	28/37 (75.7)	19/37 (51.4)	13/35 (37.1)	15/35 (42.9)
Daily dose, mg	40*	322 ± 321	390 ± 604	265 ± 307	134 ± 143

Abbreviations: OA, osteoarthritis; VAS, visual analogue scale.
Values given as mean ± standard deviation or n (%).
* Standard deviation not available because n = 1.

endpoint was met. Statistical significance was demonstrated by the fact that the change from baseline *F*-statistic for the entire study period was 18.9 ($p < .001$), and the *t*-statistic was −8.19 ($p < .001$). The decrease versus baseline value in the ankle OA VAS pain score was >25% at every timepoint, and the improvement from baseline was greatest at week 12 (Fig.).

Secondary Efficacy Analyses

Improvement versus baseline in the ankle OA VAS disability score was evident at every timepoint (Table 2). As with the pain score, the greatest improvement was evident at week 12. The LS mean change from baseline in the VAS disability score during 26 weeks was −19.2 mm (95% CI −24.8 to −13.6 mm), which corresponds to a percentage reduction of 34% (95% CI 22.3% to 45.7%). The disability score change from baseline *F*-statistic was 13.7 ($p < .001$), and the *t*-statistic for the change from baseline was −6.77 ($p < .001$). Therefore, the change was statistically significant.

A trend toward improved patient global assessment scores was observed after treatment with NASHA (Table 2). The LS mean change from baseline during the 26-week follow-up period was 3.68 mm (95% CI −3.07 to +10.44 mm), representing a percentage change of 23.9% (95% CI 5.2% to 42.6%). However, the change from baseline in the patient global assessment score was shown to not be statistically significant.

The percentage of participants using rescue medication (ie, acetaminophen) was highest at week 6 (75.7%), and the mean daily dose was highest (390 mg, range 12 to 2500 mg) at week 12. These values were lower at later timepoints: at week 26, 42.9% of participants had used rescue medication since the previous visit, and the mean daily dose was 134 (range 8 to 483) mg. Rescue medication use at baseline was available for only the small number of participants (n = 6, 16.2%) with separate clinic visits for screening and baseline. One (16.7%) of these individuals had used rescue medication at baseline (average daily dose 40 mg).

Table 3
Adverse events affecting more than 1 participant (safety set, N = 37)

Adverse Event	No. of Participants (%)
Any	28 (75.7)
Arthralgia	9 (24.3)
Headache	9 (24.3)
Nasopharyngitis	7 (18.9)
Injection site pain	6 (16.2)
Back pain	5 (13.5)
Pain	3 (8.1)
Dental caries	2 (5.4)
Injection site joint pain	2 (5.4)
Influenza	2 (5.4)
Procedural pain	2 (5.4)
Plantar fasciitis	2 (5.4)
Neck pain	2 (5.4)
Migraine	2 (5.4)

Safety

AEs were reported in 28 study participants, representing 75.7% of the safety population (Table 3). The 3 most common AEs were headache, arthralgia, and nasopharyngitis. Most AEs were of mild or moderate intensity; thus, the investigators regarded most of the AEs as minor. Five (13.5%) participants experienced 7 AEs that were considered to be related to the study treatment. Six (16.2%) of these AEs concerned the injection site (injection site pain, n = 3, 8.1%; injection site joint pain, n = 3, 8.1%), and there was 1 (2.7%) report of plantar fasciitis. One (2.7%) participant withdrew from the study prematurely at 12 weeks postinjection, and the reason for withdrawal was a treatment-related AE (ie, injection site joint pain). There was 1 (2.7%) serious AE (ie, appendicitis), which resulted in hospitalization. This AE was not considered to be related to study treatment, and the affected participant completed the study. No deaths occurred during the study.

Discussion

This is the first study of intra-articular NASHA for the treatment of ankle OA. The results demonstrate that the injection was generally well tolerated and effective in reducing symptoms. The ankle OA VAS pain score improved significantly, with a clinically meaningful 25% reduction in pain throughout the 6-month follow-up period. Statistically significant improvements were observed in the ankle OA VAS disability score. The percentage of participants using rescue medication declined after week 6.

Most AEs were common complaints of mild or moderate intensity and unrelated to study treatment. Treatment-related AEs mainly concerned the injection site and affected only a minority of the study participants. Overall, the results in this limited number of participants do not suggest any safety concerns with the intra-articular injection of NASHA for the treatment of ankle OA.

Numerous single-arm studies have reported that viscosupplementation may be effective in the treatment of OA of the ankle or subtalar joint, reducing pain and providing functional improvements (27–36). In the largest of these studies, individuals with Kellgren-Lawrence grade I/II ankle OA (n = 75) received 5 weekly injections of HA (Artz®; Sekagaku, Tokyo, Japan) and were followed for 6 months (34). Mean reductions from baseline in AOS score and the American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score (37,38) of 2.6 and 14 points, respectively, were reported 1 month after the most recent injection, with the same improvements at 6 months. The most recent of these studies assessed the impact of 3 injections of sodium hyaluronate in 50 participants with ankle OA (36). At 6 months posttreatment, statistically significant increases versus baseline in the mean Foot and Ankle Outcome Score values (39) were observed for all 5 domains (pain: 84 versus 48 points, $p = .005$). The efficacy measurements were different in our study; however, the results suggest that improvements in response to a single injection of NASHA may be similar to those observed with multiple injections of other HA preparations.

Several randomized controlled studies of viscosupplementation for ankle OA have been published (40–42). In 30 individuals with Kellgren-Lawrence grade III ankle OA, Karatosun et al (41) compared the use of 3 weekly HA injections versus exercise therapy. Statistically significant improvements from baseline in the AOFAS Ankle-Hindfoot Scale score were observed at 12 months in both groups ($p < .01$). Although the increase in the AOFAS Ankle-Hindfoot Scale score was numerically greater in the HA group, no statistically significant between-group differences were observed. In a second study involving 30 individuals with Kellgren-Lawrence grade II/IV ankle OA, 5 weekly injections of sodium hyaluronate were compared with placebo (40). At 3 months, a significantly greater percentage improvement from baseline in total AOS score was observed in the sodium hyaluronate group compared with the placebo group (36% vs 9%, $p = .04$). A nonsignificant benefit with sodium hyaluronate was also observed at 6 months (31% vs 13%). The third randomized controlled trial had 20 participants with Kellgren-Lawrence grade II/IV ankle OA (42). Five weekly injections of sodium hyaluronate were compared with placebo, and the study included a 6-month follow-up period. There were statistically significant improvements from baseline in mean AOS score in both study groups. At 6 months, 5 of 9 participants in the sodium hyaluronate group showed improvement of >30 mm, compared with 1 of 8 participants in the placebo group, but statistically significant between-group differences relating to the AOS score were not observed. Unfortunately, the overall quality of the randomized controlled trials was low and the numbers of participants were limited. As reported by the authors of a systematic review of viscosupplementation for ankle OA, although there is some evidence of superiority of viscosupplementation versus saline control, there is no evidence of significant benefit versus exercise-based therapy (11).

Intra-articular injection of HA has been shown to be well tolerated, with few AEs and no significant safety concerns. Temporary local AEs related to the injection procedure (eg, swelling, increased pain) may occur in some individuals (34,43). Comparison of intra-articular injection of sodium hyaluronate versus saline control has shown similar rates of AEs with both procedures (40). Therefore, the safety outcomes of our study are also similar to those of previous studies.

A 2015 Cochrane review (44) assessed the use of viscosupplementation for ankle OA. The authors reported uncertainty as to whether HA provides benefits versus placebo at 6 months, whether HA is superior to other treatments, which dosing schedule should be used, and which patients are likely to gain the most benefit. However, the authors stated that HA "can be conditionally recommended if patients have an inadequate response to simple analgesics." The methodological standards of the Cochrane review are high and are not attainable for most orthopedic procedures because of financial constraints. Several more recent reviews of the use of HA for ankle OA have been published, but because no clinical studies have been published since 2012, their findings are similar to those of the Cochrane review (12–14).

It is notable that NASHA can be administered via a single injection, while in studies of other HA products for ankle OA, multiple (3 to 5) injections were used. The single-injection approach is possible with NASHA because of the stabilization process that increases the intra-articular residence time (15). During manufacture, a molecular cross-linking reagent is added to purified HA under conditions controlled to achieve 0.5% to 1.0% cross-linking. This increases the molecular weight by a factor of 10^{13} and turns the HA into a 3-dimensional gel without compromising its biocompatibility. As a result, the intra-articular half-life of NASHA is approximately 4 weeks, compared with values between approximately 10 hours and 9 days for other HA products (15). Single-injection treatment is likely to be preferred by both patients and healthcare professionals, while potentially reducing treatment-associated costs.

In the United States, NASHA is approved for the treatment of OA of the knee but not for the treatment of OA of the ankle. It is, therefore, of interest to compare the effects of NASHA in the 2 settings. Studies in knee OA have reported percentage changes from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index pain score between approximately 25% and 40% at 6 weeks posttreatment (the effect of NASHA appears to peak at 6 weeks in that setting) (17,18,21). In the present study, the maximal reduction from baseline in the VAS pain score was greater (approximately 50%). Direct comparison between the results for knee OA and the results for ankle OA is confounded by several important factors (eg, use of different pain measurement scales, anatomical differences between the 2 joints, use of different injection volumes). However, it appears possible that NASHA could, on availability of more data, become an approved treatment option for ankle OA in the United States.

The principal limitation of this study is the lack of a control group. The use of rescue acetaminophen could potentially have increased the improvements from baseline, but there was no apparent correlation between pain score improvement and the dose of acetaminophen or percentage of patients taking it. The allowance of nonpharmacological therapy had the potential to reduce the study's sensitivity to the effects of NASHA. However, regimen changes in nonpharmacological therapy (apart from discontinuation) were not permitted, and only a minority (21.6%) of patients received such treatment. The inclusion of a control group (eg, placebo) might have shown how much of the change from baseline in each efficacy variable was attributable to NASHA. Strengths of the study include fulfillment of the number of participants required for statistical power, recruitment of individuals with limited symptoms in the contralateral joint (response to treatment more clearly defined), and inclusion of a variety of efficacy endpoints. Overall, despite the limitations of our investigation, we believe that the results presented here could serve as a useful platform for the future development of

prospective cohort studies and randomized controlled trials of the use of NASHA in the treatment of ankle OA.

In conclusion, the results of this prospective cohort study suggest that viscosupplementation with NASHA in the treatment of ankle OA holds promise. A single injection was associated with clinically meaningful reductions in pain and disability for up to 26 weeks and, although 1 participant reported pain and withdrew from the study, the procedure was generally well tolerated. Further investigation of NASHA for the treatment of ankle OA, including a large prospective cohort study and a randomized controlled trial, appear to be merited.

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