Intra-articular injection of non-animal stabilised hyaluronic acid (NASHA) for osteoarthritis of the hip: A pilot study

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Abstract

Objectives

This study was undertaken to assess the safety and potential efficacy of intra-articular non-animal stabilised hyaluronic acid (NASHA) in patients with hip OA.

Methods

This was a prospective, open-label, 3-month pilot study of a single intra-articular injection of NASHA in 31 patients. Safety outcomes were measured at 2 weeks and 3 months after treatment, as were efficacy measurements including WOMAC pain, stiffness and physical function scores, and the patient assessment of global disease status. Patients demonstrating reduced pain at month 3 participated in an extension phase (assessment at 6–11 months; 18 patients). Positive response was defined as a ≥40% reduction in the WOMAC pain score from baseline, together with an absolute decrease of ≥5 points.

Results

Intra-articular injection of NASHA into the hip was well tolerated. The only treatment-related AE was exacerbation of pain and/or stiffness in the treated hip (reported by 9 patients) and there were no serious AEs. The response rate to treatment was 50% at 2 weeks and 54% at 3 months. In the extension population, response rates of 69% and 44% were observed at month 3 and the extension visit, respectively. Global disease status was improved at month 3 compared with baseline in 68% of the patients.

Conclusions

Our results show that a single intra-articular injection of NASHA is a well tolerated and potentially effective therapy in the treatment of hip OA. Further studies of NASHA in this setting are warranted.

Key words

Osteoarthritis, hip, injections, intra-articular, non-animal stabilised hyaluronic acid.

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Introduction

Osteoarthritis (OA) is a chronic degenerative disease of the joints characterized by articular pain, cartilage degradation and loss of normal joint function (1, 2). OA is the most common and costly form of destructive joint disease worldwide, with OA of the hip affecting an estimated 10–15% of the elderly population over 70 years of age (3-5). The medical and socioeconomic burden of OA is likely to increase further in the coming years, with the continued growth of the elderly population in the developed world (6).

Conservative options for the treatment of OAof the hip include both non-pharmacological and pharmacological approaches (7). Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common pharmacotherapy. Although these agents have proven therapeutic efficacy, the use of NSAIDs in elderly patients may be limited by their potential for serious gastrointestinal adverse effects (8). Indeed, as many as 20–30% of all hospital admissions and deaths due to peptic ulcer disease in the elderly have been reported to be related to the use of NSAIDs (9). Cyclooxygenase-2 (COX-2) inhibitors appear to cause fewer gastrointestinal side effects than NSAIDs; however, emerging data suggest that these agents are also associated with the potential for serious adverse effects (10, 11). Intra-articular corticosteroid injections are an effective treatment option, but their duration of efficacy is typically short, necessitating frequently repeated administration. This is cause for concern, since there may be a risk of articular cartilage damage with the frequent intra-articular injections of corticosteroids (12).

Until recently, the only alternative to these conservative approaches for the treatment of hip OA has been surgery. When hyaluronic acid (HA) was introduced it appeared to offer a promising new option. HA is a polyanionic polysaccharide found naturally in the synovial fluid, which has lubricating and protective functions. The molecular weight and concentration of HA is reduced in the synovial fluid of arthritic joints, resulting in low viscosity and increased cartilage loading (13). Intra-articular injection of HA– or viscosupplementation – is recognised by current American College of Rheumatism guidelines to be an effective alternative to other conservative approaches for the treatment of OAof the knee (14). However, most available HA products have dosing regimens that require multiple injections, with efficacy that does not persist for longer than 6 months, which may limit their long-term clinical utility (13,15).

Durolane® (Q-Med; Uppsala, Sweden) is a novel HA preparation comprising non-animal stabilised HA(NASHA). It is manufactured by a two-stage procedure – biosynthesis of HA by cultured bacteria followed by a mild stabilisation process (cross-linking that is restricted to 0.5–1.0%). Stabilisation does not change the biochemical properties of the HA, but creates a biocompatible gel with improved viscoelastic properties and a longer residence time in the joint compared with non-stabilised HA preparations (16,17). This may be expected to reduce the number of injections required to achieve therapeutic effects. A single intra-articular injection of NASHA has been shown to have a favourable safety profile in the treatment of knee OA (18). This pilot study was undertaken to assess the safety, potential efficacy and duration of response following a single intra-articular injection of NASHA for the treatment of OAof the hip.

Materials and methods

Patients

Male and female patients with a diagnosis of OAof the hip according to ACR criteria (19), a WOMAC pain score of at least 7 in one hip (range of the scale 0–20), and significant hip pain for the majority of days during the previous 3 months were eligible for inclusion in this trial. Study participants were also required to be fully ambulant and to have had a hip X-ray within the past 6 months with a score of no more than Grade II or III on the Kellgren-Lawrence scale (20).

Exclusion criteria included: intra-articular injection of corticosteroids into the hip within 3 months of study entry; arthroscopy or other local surgical proce-

dures within 3 months of study entry; use of systemic corticosteroids within the past 3 months; known allergy or hypersensitivity to HA, local anaesthetics or contrast media; septic arthritis in the hip in the last 3 months; and current rheumatoid arthritis, other systemic inflammatory conditions or any other illness likely to interfere with assessment of the study medication. Patients using anticoagulants, pregnant or breast-feeding women and women of childbearing potential not using adequate contraception were also excluded from participation.

Study design

This was a prospective, open-label, single centre, pilot study. The study investigator performed the injection in all 31 patients. After removal of any effusion present, all patients received a single intra-articular injection of NASHA (3 ml; hyaluronic acid 20 mg/ml). This was administered under strict aseptic conditions using a local anaesthetic (Xylocain® [AstraZeneca Ltd, London, UK]: lidocaine hydrochloride 10 mg/ml, adrenaline 5 μg/ml), with intra-articular deposition confirmed by contrast verification (Omnipaque® [Amersham Health Ltd, Little Chalfont, UK]: iohexol 388.3 mg/ml, iodine 180 mg/ml). The injections were made using a 130 mm long 18 G needle (Beckton & Dickinson, Franklin Lakes, USA). In patients with OA of both hips, the worse affected hip (i.e. the hip with the higher baseline WOMAC pain score) was treated.

Since this represented the first time Durolane had been injected into the hip joint, the study was supervised by a safety committee. Post-treatment tolerability and safety was evaluated in the first 4 patients before additional patients were allowed to enter the study.

Clinical assessments were made at baseline, 2 weeks and 3 months; in addition, telephone follow-up at 4 weeks assessed the patients'adverse events and use of concomitant medication. An extension phase was also introduced to the study, where all patients who had shown a reduction in pain at the 3-month visit and who had not undergone hip surgery after the 3-month visit were invited to visit the clinic at approximately 6 months post-treatment. Intra-articular injection of other HA preparations or corticosteroids was not permitted during the study period. NSAID or analgesic therapy was permissible throughout the study, provided the dose was not altered within the month prior to study entry or during the study period.

The study was performed in accordance with the Declaration of Helsinki and subsequent revisions and approved by the local Independent Ethics Committee. All patients provided written informed consent.

Assessments

All adverse events (AEs) were recorded by the study investigator. The primary outcome measure was the frequency of treatment-related AEs. Efficacy was measured at baseline, 2 weeks, 3 months and approximately 6 months using the WOMAC osteoarthritis index (version 3.1, Likert format, Swedish version), the patient's assessment of global status (5-point scale from very good to very poor) and range of motion (6 components). The WOMAC index consists of 3 dimensions: pain, stiffness and physical function. Each dimension contains numerous items that are assessed on the following scale: None, Mild, Moderate, Severe, and Extreme. The score of each dimension is calculated from the sum of the scores (0–4) for each item, giving a range of 0–20 for pain, 0–8 for stiffness and 0–68 for physical function.

A post-hoc analysis was also undertaken to calculate the overall response rate according to established OA response criteria, namely the percentage of patients achieving a reduction in the WOMAC pain score of at least 40% from baseline, comprising a minimum absolute reduction of 5 points (21).

Statistical analysis

Changes in WOMAC variables from baseline at 2 weeks, 3 months were analysed by means of the paired Student's t-test. Changes in the patients' assessment of global status from baseline at these times were analysed using the McNemar test. All statistical tests were two-sided at the 5% level of significance. Not all patients participated in the extension phase; therefore the 'extension population' was analysed separately for all timepoints using the same methodology as in the primary analyses.

Results

Data were available for a total of 31 patients (16 females and 15 males), all of whom completed the 3-month study. Three of these patients received increased analgesic medication after the administration of NASHA, and these patients were omitted from the efficacy analysis to avoid the risk of bias. Therefore, the safety population comprised 31 patients, while the efficacy population included 28 patients. Eighteen patients participated in the extension phase, of whom 16 were included in the efficacy analysis. The time elapsing between treatment and the final visit for the extension population varied from 6 to 11 months (mean 7 months).

Patient demographics and clinical characteristics at baseline are summarised for the overall population (n = 31) in Table I. The mean WOMAC pain score at baseline was 11.2 (range 7–18). As shown, the majority of study participants (24/31; 77.4%) had previously received NSAID or analgesic therapy for their OA. However, only two patients had received prior intra-articular corticosteroids (2/31; 6.5%) and none had previously been treated with HA. Almost two-thirds of the patients (20/31; 65%) were treated with NSAIDs and/or analgesics at a constant dose throughout the study – 3 of these patients changed to a different but equivalent medication during the study. None of the study participants required any removal of effusion from the hip joint prior to treatment with NASHA.

Intra-articular injection of NASHAinto the hip was well tolerated, with no serious AEs reported over the 3 months of follow-up. A total of 18 AEs were reported by 13 patients, of which 16 (89%) were reported during the first 3 months post-treatment. Half of all the AEs (9/18; 50%) were deemed unrelated to therapy. All 9 treatment-related AEs were exacerbation of pain and/or stiffness in the treated hip (Table II). This

Table I. Patient demographics and clinical characteristics at baseline (overall population, n = 31).

Parameter	Value	
Gender[a]		
Male	16	(51.6%)
Female	15	(48.4%)
Age (years[b])	60.0 ± 10.1	(43.0–82.7)
BMI (kg/m^{2}[b])	26.4 ± 3.8	(20.8–34.6)
Duration of disease (years[b])	3.0 ± 4.4	(0–23.2)
Prior therapy[a]		
Analgesic or NSAID	24	(77.4%)
Glucosamine	12	(41.9%)
Intra-articular corticosteroid	2	(6.5%)
Intra-articular HA	0	
Surgery	0	
Radiological grade Kellgren Lawrence[a]		
II	16	(51.6%)
III	15	(48.4%)
Baseline disease severity[b]		
WOMAC pain score	11.2 ± 2.5	7–18
WOMAC stiffness score	4.6 ± 1.3	2–7
WOMAC physical function score	35.8 ± 9.5	19–56
Hip injected[a]		
Left	15	48.4%
Right	16	51.6%

[a]Values are expressed as number of patients (%); [b]values are expressed as the mean ± S.D. (range).

Table II. Treatment-related adverse events reported following the intra-articular injection of NASHA(safety population, n = 31).

Pt. ID	Adverse event	Day of onset	Intensity	Duration (days)	Treatment
5	Increased hip and leg pain	36	Moderate	On-going (stable)	NSAID
6	Hip and leg pain	1	Severe	22	None
7	Hip pain	0	Moderate	11	None
8	Hip pain	1	Moderate	10	None
9	Hip pain and stiffness	1	Moderate	7	None
11	Hip pain and stiffness	0	Moderate	11	None
18	Increased hip and leg pain	0	Severe	18	Analgesics
21	Intense hip pain	0	Severe	11	Reduced activity
22	Increased hip pain	3	Moderate	7	Analgesics

typically occurred within a few days of treatment and was generally of moderate intensity (increased analgesic/ NSAID medication was required by only 3 patients). With the exception of one case of on-going hip and leg pain, all of the AEs resolved during the study. No infections or other treatment-related AEs were reported.

The mean WOMAC scores for pain, stiffness and physical function at baseline, 2 weeks and 3 months are shown for the efficacy population (n = 28) in Figure 1A. Significant reductions from baseline in mean the WOMAC pain score in treated hips were seen at 2 weeks (4.8 points, $P < 0.0001$) and 3 months (5.5 points, $P < 0.0001$). Corresponding decreases in the mean WOMAC stiffness scores were 1.5 and 1.3 points at 2 weeks and 3 months, and for the WOMAC physical function the decreases were 10.9 and 15.9 points; all these decreases were statistically significant. Corresponding results for the extension population (baseline, 3 months and extension visit; n = 16) are shown in Figure 1B. The improvements at month 3 relative to baseline in WOMAC pain, stiffness and physical function were similar to those for the whole patient population. Continued efficacy during the extension phase was evident with significant benefits versus baseline for all three parameters, and a small decrease in the treatment effect between month 3 and the extension visit (month 6–11). Similar results at all timepoints were observed in the overall population (n = 31 to month 3, n = 18 for the extension phase; data not shown).

In the efficacy population, patient assessments of global status revealed that 19 (68%) considered their condition to have improved at the end of the 3 months of follow up, with only one patient (4%) indicating that they felt their condition had worsened over this period of time ($P < 0.0001$; Fig. 2A). The proportion of patients who considered their global status to be good or very good increased from zero at baseline to 46% at 3 months. For the extension population (n = 16), the majority of patients (81%) reported an improvement in global status at 3 months versus baseline (Fig.2B). Continued benefit was apparent at the extension visit, with only 1 patient (6%) reporting a worsened global status versus baseline, although the proportion of patients with improvement decreased to 38%.

The WOMAC pain scores for each individual patient at baseline, 2 weeks and 3 months are shown in Table III. These values were used to calculate the treatment response rates. In all, 14 patients (50%) were found to be treatment responders at 2 weeks and 15 patients (54%) at 3 months post-treatment. The number of patients in the extension population who demonstrated a positive response was 11 (69%) at 3 months and 7 (44%) at the extension visit. As with the WOMAC scores, similar results were observed in the overall population (n=31, data not shown).

There were major difficulties with the

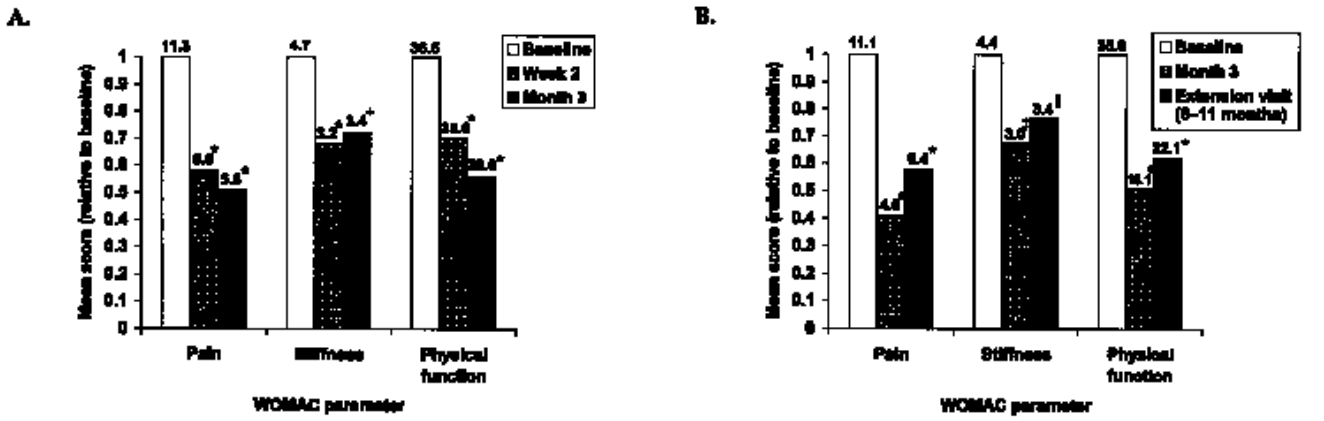

Fig. 1. Mean WOMAC scores for pain, stiffness and physical function before and after a single intra-articular injection of NASHA (**A**: efficacy population [n = 28]; **B**: extension population [n = 16]). Values are for the study hip only (*P ≤ 0.0001 vs baseline; ⁺P = 0.0007 vs baseline; ‡P = 0.0043 vs baseline; § P = 0.0013 vs baseline).

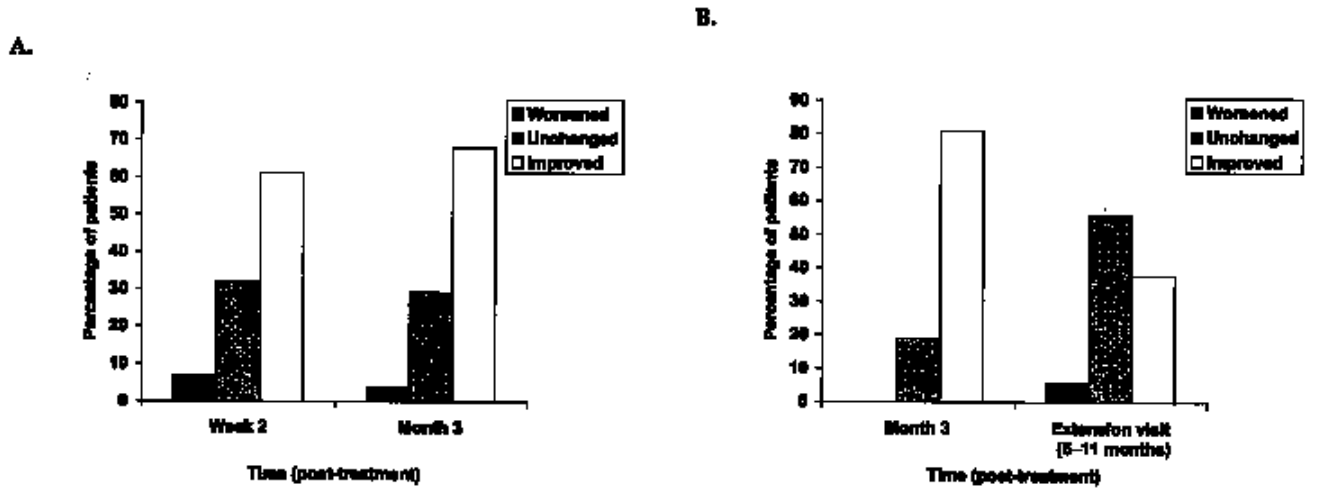

Fig. 2. Patient assessments of global status compared with baseline following a single intra-articular injection of NASHA (**A**: efficacy population [n = 28]; **B**: extension population [n = 16]).

reproducibility of all of the range-of-motion subscales, both between patients and within patients (i.e., from one visit to the next). The impression of the study investigator was that the outcomes were dependent on the patient's status on the day of the visit. Also, the type of bed used seemed to influence the results. It was therefore impossible to draw meaningful conclusions from any of the range-of-motion assessments (data not shown).

Discussion

The results of this open-label pilot study show a single intra-articular injection of NASHAto be well tolerated for the treatment of OA of the hip, with no apparent safety concerns. The most frequent treatment-related AE was arthralgia, an event commonly experienced in the natural course of OA and which was reported by a total of 9 patients. This reaction was generally transient and all patients made a full recovery, with specific medical therapy required by only 3 of the affected patients. No infections or other treatment-related AEs were reported.

Investigator and patient assessments of symptom severity suggest that a single intra-articular injection of NASHA is of potential clinical benefit, with significant improvements in the WOMAC pain, stiffness and physical function scores seen at 2 weeks and 3 months. Benefits were also evident during the extension phase, although the extension population was selected on the basis of an improvement in pain at 3 months. The extension visit response rates should not, therefore, be interpreted as an indication of the overall response at 6–11 months. The efficacy findings should be considered in the light of the limitations of the design of this preliminary study. While it is unlikely that placebo would produce such long-lasting benefits, the open design, lack of a control group, and small number of patients mean that the extent of

Table III. WOMAC pain scores for individual patients at each clinic visit (efficacy population, n = 28).

Pt. ID	WOMAC pain score Baseline	2 weeks	3 months	Extension visit
1	8	2	4	0
2	10	4	5	8
3	7	2	10	-
4	12	6	6	9
6	17	13	7	13
7	11	9	8	-
8	13	13	11	15
9	10	6	10	-
10	11	5	7	3
11	12	4	1	2
12	12	13	5	-
13	9	6	5	6
14	10	3	3	11
15	12	14	6	9
16	13	7	10	11
17	12	6	12	-
19	18	4	3	-
20	13	8	2	-
21	10	12	3	7
23	10	2	7	-
24	12	1	4	-
25	13	9	10	-
26	11	5	1	2
27	13	4	0	3
28	8	3	2	3
29	12	9	11	-
30	8	7	2	0
31	8	4	6	-

the genuine treatment effect cannot be assessed. It is known from experience with knee OA that the placebo effect with viscosupplementation tends to be substantial (13), so comparison of NASHA with placebo will be required to confirm the efficacy of this treatment for hip OA.

Experience with intra-articular HA products for the treatment of OAof the hip is currently limited, with the results of only a small number of open-label studies published to date. In one study of 44 patients with hip OA who received between 3 and 5 intra-articular injections of Hyalgan® (Fidia SpA, Padua, Italy) at weekly intervals, 68% reported reduced pain and improved range of motion at 3 months (22). Improvements in the VAS pain scores were also seen in a further study of 30 patients treated with 5 weekly injections of sodium hyaluronate (2 ml/20 mg per injection) (23). Preliminary data for 50 patients with hip OAtreated with hylan G-F 20 showed half of all patients to be symptom-free (VAS pain score < 20 mm) at follow-up (24). Similarly, 50% of 22 patients were considered to be treatment responders, defined as a 50% reduction in the Lequesne score, 1 month after their first intra-articular injection of hylan G-F 20 in a more recent trial (the response rate 1 month after treatment increased to 59% after the administration of a second injection to non-responders) (25). Our results, demonstrating a positive response that was sustained for at least 3 months after treatment in 55% of patients (and for a further 3–8 months in 44% of the extension population), compare favourably with these data. A crucial difference, however, is that we studied the results of a single injection of NASHA whereas multiple injections were administered with other HApreparations. Viscosupplementation is recognised by the ACR as an effective alternative to other pharmacological approaches for the treatment of OA of the knee (14), but has not yet been recommended for hip OA due to the lack of supportive evidence from randomised, controlled clinical trials. However, it is our belief that NASHA is likely to be as beneficial in patients with OA of the hip as those with affected knees – the findings of the present study support this hypothesis. The principal benefits of NASHA compared with conventional pharmacological approaches such as NSAIDs are the chance for long-term pain relief from a single, well-tolerated injection procedure eliminating the need for daily treatment. The lack of necessity for courses of multiple injections distinguishes NASHA from other HA preparations; improvements in patient convenience and the cost-effectiveness of intra-articular treatment can therefore be expected.

In summary, the results of this open-label, pilot study show a single intra-articular injection of NASHA to be well tolerated for the treatment of OA of the hip, and also indicate notable potential symptomatic benefits. Further studies of NASHA in this setting are clearly warranted.

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