Clinical Effects of Intraarticular Injection of High Molecular Weight Hyaluronan (Orthovisc®) in Osteoarthritis of the Knee: A Randomized, Controlled, Multicenter Trial

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of injection of high molecular weight (HMW) hyaluronan (Orthovisc®) in patients with mild, moderate, and severe knee osteoarthritis (OA).

Methods. A randomized, arthrocentesis-controlled, multicenter trial. Patients (n = 372) were randomized to 4 weekly HMW hyaluronan injections (O4, n = 128), 3 weekly HMW hyaluronan injections followed by one arthrocentesis (O3A1, n = 120), or 4 arthrocenteses without injection (control group, A4, n = 124). All patients had knee OA, as determined by Kellgren-Lawrence (K-L) grade, and Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain score ≥ 200 mm and < 400 mm in index knee and < 150 mm in contralateral knee. The primary outcome measure was the proportion of patients achieving a 20% relative and 50 mm absolute improvement from baseline in WOMAC pain score at Weeks 8, 12, 16, and 22 post-baseline in the index knee. Secondary outcomes were Patient Global score, Investigator Global score, and Pain on Standing score.

Results. The evaluable subgroup consisted of patients with K-L grade 2 or 3 at baseline. The comparison of O4 versus A4 for the primary outcome approached, but did not reach, significance in the evaluable subgroup: 76% of O4 patients had ≥ 20% improvement in WOMAC pain score at Week 8 compared to 62% of A4 patients. More O4 patients had ≥ 40% improvement in WOMAC pain score compared to A4. The effectiveness of the 3-injection regimen (O3A1) was masked by a possible placebo effect from the needle injection procedure in the A4 (control) group. No differences between groups were observed with respect to incidence of adverse events.

Conclusion. Our findings indicate that HMW hyaluronan is safe and seems to be effective in the treatment of mild to severe OA of the knee. (J Rheumatol 2005;32:1928–36)

Key Indexing Terms:
OSTEOARTHRITIS HIGH MOLECULAR WEIGHT HYALURONAN CLINICAL TRIAL

Osteoarthritis (OA) is the most common rheumatic disorder and the leading cause of disability in adults over age 45 years[1]. At least 21 million Americans have OA[2]. As the population ages, the number will exceed 32 million, according to data from the Centers for Disease Control and Prevention[1]. Knee OA is extremely common, and some population surveys show that radiologically confirmed OA of the knee occurs in at least 30% of persons after the age of 50 years, and up to 80% of people older than 75 years[3]. It is estimated that in the US about 100,000 people with OA of the knee are unable to walk independently from bed to bathroom[1]. Roughly 300,000 knee joints were surgically replaced during 1995[2]. The traditional belief that OA is simply a "wear and tear" condition associated with aging is no longer tenable. New knowledge on cartilage and the pathogenesis of OA has fostered interest in additional approaches for prevention and treatment of OA.

The current treatment recommendations for knee OA[4] include nonpharmacologic measures, such as weight reduction when needed, and other measures that reduce load and impact on the knees, such as the use of high stools and high chairs, walking aids (canes, crutches, walkers) and quadriceps strengthening exercises (isometric quad drill) on a regular basis. After the basic management program is estab-

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lished, the next step is the addition of medications including non-opioid analgesics, nonsteroidal antiinflammatory drugs (NSAID), and judicious use of intraarticular (IA) corticosteroid therapy. Numerous traditional (nonselective) cyclooxygenase (COX-1) and COX-2-specific NSAID agents are available. IA corticosteroid injection therapy is often successful in knee OA associated with synovitis or effusion. IA hyaluronan (hyaluronate, hyaluronic acid) therapy is another therapeutic approach for knee OA unresponsive to conventional measures in patients who have difficulty coping with pain and activities of daily living. IA high molecular weight (HMW) hyaluronan injection offers an additional approach for patients who wish to delay or avoid knee joint replacement surgery.

Hyaluronan (HA), a glycosaminoglycan mainly responsible for the viscosity and lubrication of normal synovial fluid, has been studied as a substance capable of possibly restoring the normal properties of synovial fluid and cartilage and reducing pain and stiffness in the OA knee[5,6]. Several preparations — HMW hyaluronan (Orthovisc®, molecular weight 1 to 2.9 million Da), sodium hyaluronate (Hyalgan®, molecular weight 500,000 to 730,000 Da; Supartz®, molecular weight 620,000 to 1.17 million Da), and hylan G-F20 (Synvisc®, cross-linked) — approved by the US Food and Drug Administration are currently available in the US, Canada, and Europe[7-10]. These preparations require 3 (Synvisc®) to 5 (Hyalgan®, Supartz®) IA injections[8-10].

This therapeutic approach has been called viscosupplementation, because initially clinical improvement was thought to be due to supplementing the viscous properties of altered pathologic synovial fluid[11,12]. It may also have a beneficial protective effect on the chondrocyte, with structure-modifying improvement. The mechanism of action may include antiinflammatory effects such as inhibition of phagocytosis[13,14], chemotaxis[15], prostaglandin synthesis[16], and removal of oxygen-free radicals[17].

Significant adverse effects are limited to rare acute local reactions, which have occurred only after injection of the cross-linked hylan G-F20 preparation (Synvisc®). This so-called "pseudo-septic" reaction[18-20] has been reported in about 2% to 8% of patients injected with Synvisc® [21-23]. No similar reactions have been reported with use of other non-cross-linked purified preparations, including Orthovisc® [24].

Structural disease modifying activity has been postulated for hyaluronate injectable therapy, but has not been confirmed in human subjects with knee OA. A recent one-year study[25] investigated structural changes by measuring change in joint space narrowing. Jubb, *et al*[25] reported less progression of joint space narrowing in patients treated with hyaluronan compared to placebo. This occurred especially in subjects with milder radiologic disease at baseline. Such data suggest a possible strategy for early "preventive" treatment of OA of the knee.

The results of previous hyaluronate studies[26-28] led to the conclusion that IA HA is a worthwhile treatment option to consider in difficult to treat patients with moderate to severe OA of the knee [Kellgren-Lawrence (K-L) grades 2 or 3]. Neustadt[28] reported the potential for significant clinical improvement is considerably diminished in patients with advanced (endstage) disease and severe radiographic changes (K-L grade 4). These patients, with so-called "bone on bone" disease, usually will require surgical knee replacement[29].

We evaluate the efficacy and safety of 3 or 4 injections of HMW hyaluronan (Orthovisc®) in patients with OA of the knee in a randomized, arthrocentesis-controlled, multicenter trial. We hypothesized that Orthovisc®, a HMW hyaluronan (1 to 2.9 million Da), could require fewer injections to achieve the same effectiveness as other hyaluronans.

MATERIALS AND METHODS

Study design. A randomized, arthrocentesis-controlled, double-blind, multiple dose (3 or 4 injections) clinical trial of highly purified, HMW hyaluronan (Orthovisc®) was carried out at 24 sites in the United States and Canada during the period January 2001 to December 2002.

Patient eligibility was evaluated during a screening visit before entry into the study. To ensure patients were blinded to their treatment group assignment, each patient in each treatment group received 4 injections. Qualified participants (n = 372) were randomized with equal probability into one of 3 treatment regimens: 4 HMW hyaluronan injections (O4, n = 128), 3 HMW hyaluronan injections plus one control (arthrocentesis only) procedure (O3A1, n = 120), or 4 control (arthrocentesis only) procedures (A4, n = 124). Patients in the O4 group received 4 injections at weekly intervals of HMW hyaluronan; patients in O3A1 received 3 weekly injections of HMW hyaluronan followed by one arthrocentesis procedure; patients in the A4 group received 4 "control" (arthrocentesis only) procedures into the index knee. Four arthrocentesis procedures were used as a control group only for purposes of the study. Multiple arthrocenteses are not used as a standard treatment for OA. No injection was administered after arthrocentesis in the O3A1 or A4 patients.

To mask treatment identity and insure treatment blinding the study materials were prepackaged in a sealed patient-specific kit. Each study site had a treating (injecting) physician and a "masked observer." The masked observer performed the patient assessments including the physical evaluation, various pain scores, and safety assessments.

The protocol was approved by the appropriate institutional review boards of each institution. Informed consent was obtained from all subjects prior to participation in the study.

HMW hyaluronan. Two milliliters (30 mg) of HMW hyaluronan (Orthovisc®, molecular weight 1.0 to 2.9 million Da) were administered by IA injection. The hyaluronan was purified from rooster combs and manufactured under current good manufacturing practices[30].

Intraarticular injections. All injections were administered by either lateral or medial approach after the instillation of 1% lidocaine hydrochloride solution. Before any treatment, the joint space was aspirated to dryness, if fluid was present. Aspiration was attempted at all treatment visits. If the study involved HMW hyaluronan, the aspirate syringe was replaced with the study syringe, leaving the needle in place, and the HMW hyaluronan was injected into the IA space. For arthrocentesis control patients, the needle was left in the IA space for 5 to 10 s to simulate injection. This time approximates the duration of an injection containing active medication.

Study protocol. The study protocol required 10 patient visits, including the screening visit. Potential study participants returned for a baseline visit after washout of NSAID and analgesics (Week 0). At the baseline visit,

patients who met the enrollment criteria were randomly assigned to one of the 3 treatment groups and received the first of the series of the IA study treatments. Participants then returned for 3 consecutive weeks (Weeks 1, 2, 3) to receive one additional knee injection or arthrocentesis procedure each week. Patients also returned for followup evaluation at Weeks 8, 12, 16, 22, and 28 after the first injection. The total duration of the study was 28 weeks.

Study participants completed the Western Ontario and McMaster Universities (WOMAC) pain score, the Patient Global score, and the Pain on Standing score at screening and at Weeks 1, 2, 3, 8, 12, 16, 22, and 28. Acetaminophen, up to 4 g/day, was the only rescue pain medication allowed. Acetaminophen was not permitted for at least 24 h prior to each study assessment session.

Participant enrollment. The radiographic eligibility of the patient was assessed using the K-L grading criteria[31]. Assessment included a history, physical examination (range of motion, presence of synovitis or effusion), and a standing anterior-posterior radiograph (or semiflexed weight-bearing flexion view). During screening, patients completed a WOMAC Pain Score to assess the level of pain, stiffness, and functional impairment in each knee separately. In addition, each patient completed the Patient Global score and Pain on Standing score and the masked observer completed the Investigator Global score.

All patients were ≥ 40 years of age and were willing to discontinue all analgesics and NSAID 7 days before the first injection and for the duration of the study. All patients had a diagnosis of knee OA according to the American College of Rheumatology criteria[4], a K-L grade of 1, 2 or 3 in accord with radiographic evidence of knee OA[31], and a summed WOMAC Pain Score[32] ≥ 200 mm and < 400 mm (maximum possible score 500 mm) in the index (treated) knee and < 150 mm in the contralateral (untreated) knee.

Exclusion criteria included patients who initiated an exercise or physical therapy program within 3 months, oral or parenteral corticosteroid use within 30 days, IA injection of steroids into the index knee within 90 days, IA injection of any hyaluronic substance within the past 9 months, or operative arthroscopy within 6 months; treatment with anticoagulants; and clinically significant comorbidity (fibromyalgia, peripheral neuropathy, vascular insufficiency, or hemiparesis) severe enough to interfere with accurate evaluation.

Major protocol violations included surgery, new medications for additional conditions, initiation of a new physical therapeutic or exercise regimen, and use of proscribed medications. Patients were said to be noncompliant when they missed any patient visit (injection or followup visit).

Outcome measures. Treatment results were assessed during each patient visit. The primary outcome was the proportion of patients achieving at least a 20% relative improvement and an absolute improvement of at least 50 mm from baseline in WOMAC Pain Score over 4 assessment points between Weeks 8 and 22 in the index knee. A questionnaire was used to measure individual WOMAC Pain Scores related to 5 conditions under which the patient might experience pain: (1) walking on a flat surface; (2) going up or down stairs; (3) at night in bed; (4) sitting or lying; (5) standing upright. Each of the 5 conditions under which the patient might experience pain was scored using a visual analog scale (VAS) that ranged from 0 mm (no pain) to 100 mm (extreme pain). The WOMAC Pain Score consisted of the sum of these 5 individual 100 mm VAS scores, resulting in a maximum possible score of 500 mm.

Secondary outcome measures included the Patient Global score, Investigator Global score, and Pain on Standing score. Each of these scales used the same VAS, ranging from 0 to 100 mm.

Safety assessment. The safety of treatment was determined from adverse event reports, records of vital signs, and clinical laboratory tests. Adverse events were monitored continually during the 28 week trial and were categorized by frequency, severity, body system, treatment group, and relationship to study procedure, as determined by the investigator. The MedDRA 3.0 coding system (MedDRA, version 3.0, AutoCode CS; TRW Inc., Lyndhurst, OH, USA) was used to classify adverse events.

Calculation of sample size. The sample size calculation was based on the proportion of patients expected to achieve a clinically significant reduction in WOMAC Pain outcomes. In a previous study[21], about 60% of patients receiving saline injections and 70% of patients receiving 3 injections of HMW hyaluronan achieved a 20% (and 50 mm) reduction in WOMAC Pain scores. For arthrocentesis, it was hypothesized that approximately 55% of patients would achieve this level of pain reduction in contrast to the 60% seen for saline injections. To detect this difference between arthrocentesis and the 2 HMW hyaluronan injection series (3 injections and 4 injections), a sample size of 107 patients per group was required for 80% power and overall 5% Type I error in a 2-sided hypothesis test. This study enrolled at least 120 patients per group to allow for a loss of about 10% of randomized patients. Sample size was computed using a 2.5% Type I error to represent the Hochberg adjustment for the comparison of the O4 regimen to the O3A1 regimen and to the A4 group.

Randomization. A balanced block design was used and patient randomization was stratified by sex. Quintiles Inc. (Mt. Laurel, NJ, USA) was responsible for generation of the randomization code, packaging of the study material into kits, and distribution to sites. The investigational sites received packaged, numbered kits separately. The next eligible patient was assigned the lowest numbered available kit according to sex.

Statistical methods. Chi-square p values were used to analyze differences among treatment groups at each timepoint, and a generalized estimating equation (GEE) model was used to assess changes over time among treatment groups. GEE models tested for treatment differences while controlling for sex, time, and treatment by time interaction to test if treatments separated over post-baseline observations. In addition, if site or site by treatment interactions were statistically significant, these terms were kept in the model. All GEE models were based on the observed data. Study success was defined as a statistically significant difference among treatment groups.

The planned analyses were conducted with respect for the null hypothesis. The null hypothesis was no treatment difference in the mean trend over time (Weeks 8 to 22 inclusive) among the control group (A4) and either or both of the 2 HMW hyaluronan groups (O4 and O3A1) of the proportion of patients achieving at least a 20% level of improvement and an absolute improvement of at least 50 mm from baseline in WOMAC Pain score. The alternative hypothesis was a difference in the mean trend over time among the groups. The Hochberg procedure was used to control the overall Type I error at 5%. The p values were computed for O4 and O3A1 versus A4 and then ranked as more significant (lesser of the p values) and less significant (greater of the p values). If the greater p value was below 0.05, then significance was to be claimed for both comparisons to A4; if the greater p value exceeded 0.05, then significance could still be declared for the more significant comparison if the smaller p value was less than 0.025.

A baseline factor analysis was used to compare the baseline characteristics of the treatment groups. Baseline values were defined as those obtained at the baseline visit (before first treatment). Differences among treatment groups were tested using a one-way ANOVA for continuous measures, a Wilcoxon rank-sum test for ordinal measures, and a chi-square test (or Fisher's exact test, as appropriate) for unordered categorical measures. Global differences among treatment groups were considered statistically significant if the 2-sided p value was less than 0.05.

Post hoc analyses were conducted to determine the proportion of patients achieving a 40% and 50% level of improvement in WOMAC Pain score.

Intent to treat population. All patients who received at least one IA injection or control treatment were included in the intent to treat and safety analyses.

Evaluable population. The evaluable population was defined as patients who received all 4 treatments and at least one followup visit and who had no significant protocol deviation. The evaluable population was considered the primary planned analysis population.

Evaluable subgroup. The evaluable subgroup was a subgroup of the evalu-

able population and consisted of patients with baseline K-L grade 2 or 3 (moderate to severe) radiographic findings and contralateral knee WOMAC Pain score < 150 mm. This subgroup, eliminating patients with K-L grade 1 radiographic findings, was identified for supplemental analysis because patients with K-L grade 1 do not have confirmed OA and were not considered to be an appropriate population for HA treatment. The supplemental analysis repeated all previous analyses on this subgroup, including a summary of baseline variables and demographics, GEE analysis of improvement at 20% (plus 50 mm improvement), 40% and 50% thresholds, and GEE analysis of the secondary endpoints (WOMAC Pain scores, Pain on Standing, Investigator Global score, and Patient Global score). Calculations of Fisher's exact p values for overall differences in proportions among the treatment groups and pairwise comparisons were conducted. Asymptotic 2-sided 95% confidence intervals for the difference in the proportion achieving a response were calculated. Changes from baseline were analyzed at each timepoint using ANOVA; 95% CI about the difference in the mean change in each score were calculated.

RESULTS

Patient demographics and baseline disease characteristics. The 370 patients (128 O4, 119 O3A1, and 123 A4) who received at least one IA injection constituted the intent to treat population. Of these, the 336 patients (115 O4, 107 O3A1, and 114 A4) who completed all 4 treatments and at least one followup visit and had no significant protocol deviation constituted the evaluable population.

Evaluable population. The demographic and baseline (summed WOMAC Pain score, Patient Global score, Investigator Global score, and Pain on Standing score) characteristics of the evaluable cohort indicate no differences among the 3 treatment groups (Table 1). Mean WOMAC Pain scores for the index knee at baseline were comparable in the treatment groups (286.6 ± 60.8 in the O4 group, 289.0 ± 50.4 in the O3A1 group, and 294.1 ± 58.6 in the A4 group). Baseline mean WOMAC Pain scores for the contralateral knee were also comparable among the 3 treatment groups.

Table 1. Patient demographics and baseline disease characteristics of evaluable population.

Characteristic	Treatment Group O4 n (%)	O3A1 n (%)	A4 n (%)
No. of patients	115	107	114
Mean age, yrs	58.4 ± 8.9	58.9 ± 8.9	59.1 ± 8.3
Sex			
Male	63 (54.8)	55 (51.4)	57 (50.0)
Female	52 (45.2)	52 (48.6)	57 (50.0)
Body mass index, kg/m^2	28.9 ± 4.2	29.6 ± 4.3	29.4 ± 4.2
Radiographic evaluation, K-L grade			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	11 (9.6)	17 (15.9)	14 (12.3)
2	56 (48.7)	58 (54.2)	53 (46.5)
3	48 (41.7)	32 (29.9)	47 (41.2)
4	0 (0.0)	0 (0.0)	0 (0.0)
Mean analgesic usage, tablets/day	2.08 ± 1.8	2.48 ± 2.2	2.05 ± 2.0
Mean WOMAC Pain Score			
Index knee	286.6 ± 60.8	289.0 ± 50.4	294.1 ± 58.6
Contralateral knee	66.8 ± 47.4	69.3 ± 46.9	64.6 ± 47.9
Mean patient global score	67.5 ± 15.0	62.4 ± 15.8	64.4 ± 15.5
Mean pain on standing score	65.2 ± 17.9	65.7 ± 16.1	65.5 ± 16.1
Mean investigator global score	58.8 ± 14.5	57.0 ± 14.0	57.6 ± 14.3
Mean synovial fluid volume, ml	0.9 ± 2.73	1.0 ± 3.24	0.9 ± 3.13

The majority of patients in each treatment group had radiographic evidence of OA in both knees. The distribution of patients by K-L grade was similar for all groups: K-L grade 1%–12.5%, 2%–56%, and 3%–43%, respectively. Use of acetaminophen for knee pain was about 2 tablets per day in all groups.

Discontinuation of treatment. The intent to treat population that completed the 28 week study consisted of 128 patients in the O4 group, 119 in the O3A1 group, and 123 in the A4 group. The most frequent cause of discontinuation was worsening of symptoms, which occurred in 9 patients in the O4 group, 8 in the O3A1 group, and 15 in the A4 group (control group). Sixteen patients were lost to followup and 8 patients were discontinued because of noncompliance. No significant differences existed among treatment groups with respect to reasons for discontinuation.

Effect of hyaluronan on knee pain, stiffness, and function

Evaluable population. Within each treatment group (O4, O3A1, A4) of the evaluable population (n = 336), a statistically significant ($p < 0.0001$) improvement from baseline was observed for all endpoints (WOMAC, Pain on Standing score, Investigator Global score, Patient Global score). Among treatment groups, all endpoints indicated clinical improvements in patients receiving HMW hyaluronan, even though these differences did not reach statistical significance.

The changes from baseline scores for all endpoints compared across the 3 treatment groups are shown in Table 2. The mean change for WOMAC Pain scores was greater in the O4 group compared to the A4 group at Week 8 (–144.7 vs –126.0), Week 12 (–146.2 vs –129.5), Week 16 (–145.5 vs –125.8), and Week 22 (–123.7 vs –111.8). The mean changes from baseline for Investigator Global score were statistically significant for the O4 group compared to the A4 group at Weeks 8 and 12. The mean change (improvement) in the O4 group exceeded that of the A4 group at each assessment. The Pain on Standing score improved by > 25 mm for all 3 treatment groups at all assessment points (Figure 1). The O4 group changed more than the A4 group, but this response was not statistically significant. The Patient Global score mean change (improvement) from baseline was significant ($p = 0.0222$) at Week 8 (–37.4 mm, O4 group; –28.8 mm, A4 group). This continued at Weeks 12 and 16, with significant changes in the O4 treatment group (Week 12 –38.3 mm; Week 16 –36.3 mm) compared to the A4 group (Week 12 –28.2 mm; Week 16 –28.2 mm).

The mean daily consumption of acetaminophen during

Table 2. Treatment outcomes: change from baseline (evaluable population).

Endpoint	Group	No. of Patients	Baseline	Week 8	Week 12	Week 16	Week 22
WOMAC	O4	115	286.6 ± 60.8	–144.7 ± 113.3	–146.2 ± 119.3	–145.5 ± 119.1	–123.7 ± 123.4
	O3A1	107	289.0 ± 50.4	–113.1 ± 121.9	–121.0 ± 120.5	–121.1 ± 123.2	–108.4 ± 124.6
	A4	114	294.1 ± 58.6	–126.0 ± 120.2	–129.5 ± 121.7	–125.8 ± 117.6	–111.8 ± 117.0
Investigator global score	O4	115	58.8 ± 14.5	–27.9 ± 22.4*	–29.1 ± 23.5*	–25.4 ± 22.9	–21.7 ± 24.2
	O3A1	107	57.0 ± 14.0	–21.9 ± 25.5	–22.7 ± 24.0	–23.0 ± 23.2	–18.3 ± 26.3
	A4	114	57.6 ± 14.3	–21.6 ± 20.9	–20.7 ± 21.1	–20.0 ± 23.4	–16.0 ± 21.8
Patient global score	O4	115	67.5 ± 15.0	–37.4 ± 28.0*	–38.3 ± 28.5*	–36.3 ± 29.1*	–33.4 ± 29.1
	O3A1	107	62.4 ± 15.8	–29.0 ± 30.8	–28.2 ± 30.4	–27.5 ± 30.2	–26.1 ± 30.6
	A4	114	64.4 ± 15.5	–28.8 ± 25.6	–28.2 ± 26.7	–28.2 ± 27.0	–26.2 ± 27.5

* Indicates significant difference between treatment group (O4) and control group (A4). P value < 0.05.

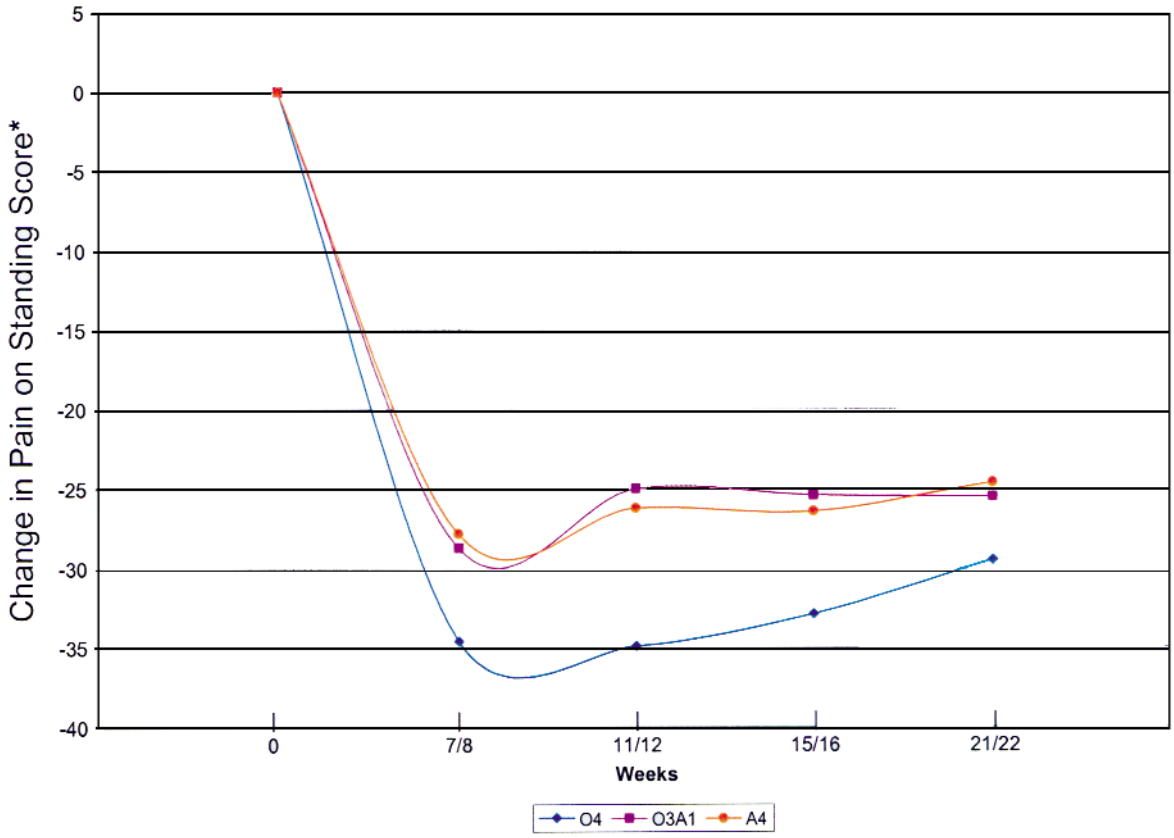

Figure 1. Mean change in Pain on Standing score. *Average baseline score: O4 = 64.8; O3A1 = 65.4; A4 = 65.9.

the study was comparable among the 3 treatment groups and ranged from 1.23 to 1.77 tablets per day.

Evaluable subgroup. The evaluable subgroup consisted of patients with a K-L grade 2 or 3 at baseline. These are considered to be most representative of candidates for viscosupplementation therapy. This group comprised 294 patients or 87.5% of the evaluable population. Patients with K-L grade 2 represented 53.8% of the O4 subgroup, 64.4% of the O3A1 subgroup, and 53% of the A4 subgroup; K-L grade 3 patients were 46.2%, 35.6%, and 47%, respectively.

The patients in the O4 group showed a significantly higher degree of improvement at Week 8 (p = 0.0320, 95% CI –66.1, –3.0) and Week 16 (p = 0.0447, 95% CI –65.2, –0.8) than the A4 group. Table 3 shows the magnitude of improvement in the WOMAC Pain scores for the index knee, relative to the baseline value. Seventy-six percent of O4 patients had ≥ 20% improvement in WOMAC Pain score at Week 8, compared to 62% of patients in the A4 group (p = 0.0346). Similar, but not statistically significant, trends were observed for the O4 group at all other timepoints at the 20% threshold.

Statistical significance was observed at higher thresholds

Table 3. Number of patients with percentage improvement from baseline in WOMAC pain scores by treatment group (evaluable subgroup).

	Percentage Improvement								
	20%			40%			50%		
	O4 (n = 104) n (%)	O3A1 (n = 90) n (%)	A4 (n = 100) n (%)	O4 (n = 104) n (%)	O3A1 (n = 90) n (%)	A4 (n = 100) n (%)	O4 (n = 104) n (%)	O3A1 (n = 90) n (%)	A4 (n = 100) n (%)
Week 8	79 (76)*	57 (63)	62 (62)	68 (65)*	47 (52)	51 (51)	62 (60)*	41 (46)	42 (42)
Week 12	79 (76)	56 (62)	67 (67)	72 (69)*	47 (52)	52 (52)	60 (58)	41 (46)	50 (50)
Week 16	89 (77)	61 (68)	67 (67)	70 (67)*	49 (54)	47 (47)	60 (58)*	42 (47)	43 (43)
Week 22	72 (69)	59 (66)	62 (62)	62 (60)*	45 (50)	45 (45)	55 (53)	38 (42)	39 (39)

* Indicates significant difference between treatment group (O4) and control group (A4). P value < 0.05.

(40% and 50%) of WOMAC Pain score improvement (Table 3). A statistically significantly greater proportion of O4 patients had a 40% improvement in WOMAC Pain scores compared to the A4 group at each week of followup (8, 12, 16, and 22 weeks) and a 50% improvement at Weeks 8 and 16. The 40% threshold showed a pronounced distinction between the O4 group and the A4 group at Weeks 12 and 16. At all weeks, 14% to 20% more O4 patients reached the 40% threshold than A4 patients.

The change from baseline scores for the Pain on Standing score, Investigator Global score, and Patient Global score was compared across treatments (Table 4). The change from baseline in Pain on Standing score between the O4 group and the A4 group was statistically significant at Week 12 (Table 4). The change in Investigator Global score and Patient Global score was significantly ($p < 0.05$) better for O4 patients than A4 patients at Weeks 8, 12, and 16. The Week 22 comparison neared statistical significance ($p = 0.0605$ Investigator Global score; $p = 0.0514$ Patient Global score).

The data indicate the O4 group produced better clinical outcomes than the A4 group. Because the A4 group achieved a better than expected improvement, no statistical differences were seen between the A4 group and the O3A1 group. The A4 group showed a strong placebo effect.

Safety profile of HMW hyaluronan

Intent to treat population. All patients who received one IA injection or control treatment were included in the safety analysis. The adverse event profiles of the 3 treatment groups are shown in Table 5. Seventy-five patients in the O4 group (58.6%), 61 in the O3A1 group (51.3%), and 65 in the A4 group (52.8%) reported 201 adverse events. The most frequently reported adverse events were headache, nasopharyngitis, arthralgia, and back pain. A total of 21 (5.7%) patients reported arthralgia; this included 16 patients in the O4 group, 4 in the O3A1 group, and one in the A4 group.

Potential device-related adverse events were reported in 11 patients in the O4 group, 6 in the O3A1 group, and 4 in the A4 group. Adverse events directly related to the injection site (erythema, bruising, or pain) consisted of 5 events in 5 patients in the O4 group, 2 events in 2 patients in the O3A1 group, and 2 events in 2 patients in the A4 group. One patient in the A4 control group reported severe injection site pain; all other injection site events were considered slight to moderate. One patient in the O4 group reported severe joint swelling that was thought to be treatment-related.

Potentially serious adverse events were reported by 4 patients in the O4 group and 3 patients in the A4 group. These adverse events included angina, myocardial infarction, gastrointestinal (GI) hemorrhage, and GI tract cancer.

Table 4. Treatment outcomes: change from baseline (evaluable subgroup).

Endpoint	Group	No. of Patients	Baseline	Week 8	Week 12	Week 16	Week 22
Pain on standing	O4	104	64.8 ± 18.4	–34.6 ± 28.3	–34.9 ± 30.0*	–32.9 ± 30.6	–29.5 ± 31.4
	O3A1	90	65.4 ± 16.9	–28.7 ± 28.8	–25.0 ± 29.1	–25.4 ± 29.6	–25.5 ± 30.2
	A4	100	65.9 ± 15.8	–27.8 ± 29.7	–26.2 ± 27.9	–26.4 ± 28.1	–24.6 ± 29.9
Investigator global score	O4	104	58.8 ± 14.3	–28.3 ± 22.5*	–29.3 ± 23.9*	–25.7 ± 22.9*	–22.0 ± 24.7
	O3A1	90	58.2 ± 14.3	–24.1 ± 24.5	–22.7 ± 24.6	–23.1 ± 23.7	–19.7 ± 27.1
	A4	100	57.8 ± 14.7	–20.6 ± 20.7	–19.2 ± 20.5	–18.4 ± 23.1	–15.4 ± 21.7
Patient global score	O4	104	67.3 ± 14.9	–38.4 ± 27.6*	–38.8 ± 28.4*	–37.3 ± 27.9*	–33.3 ± 28.6
	O3A1	90	62.4 ± 16.5	–29.6 ± 30.9	–26.5 ± 30.9	–26.2 ± 30.2	–25.5 ± 30.8
	A4	100	64.3 ± 14.9	–27.2 ± 25.8	–26.3 ± 26.1	–26.6 ± 27.2	–25.4 ± 27.3

* Indicates significant differences between treatment group (O4) and control group (A4). P value < 0.05.

Table 5. Adverse events reported by ≥ 1% of patients (by body system): intent to treat population.

Adverse Event*	O4 (n = 128) Patients, n (%)	O3A1 (n = 119) Patients, n (%)	A4 (n = 123) Patients, n (%)
Gastrointestinal	10 (7.8)	11 (9.2)	10 (8.1)
General body**	8 (6.3)	13 (10.9)	9 (7.3)
Infections	27 (21.1)	22 (18.5)	23 (18.7)
Musculoskeletal	35 (27.3)	23 (19.3)	21 (17.1)
Nervous system	20 (15.6)	18 (15.1)	26 (21.1)
Psychiatry	1 (0.8)	1 (0.8)	2 (1.6)
Respiratory	5 (3.9)	4 (3.4)	5 (4.1)
Skin	3 (2.3)	1 (0.8)	4 (3.3)

* No significant differences ($p < 0.05$) were found among the groups.
** Includes injection site erythema, edema, and pain.

None of the serious adverse events were considered by the investigator to be related to Orthovisc® treatment. No unanticipated adverse device effect occurred during the study. There were no patient deaths during the study.

DISCUSSION

Intraarticular hyaluronan injections are an alternative therapeutic option for OA of the knee. IA hyaluronan injections may provide clinical benefit to patients over the long term by improving joint function and avoiding the potential GI, cardiovascular, and renal side effects associated with chronic NSAID therapy[33,34].

We evaluated the efficacy and safety of 3 or 4 injections of high molecular weight hyaluronan (Orthovisc®) in patients with OA of the knee in a randomized, arthrocentesis-controlled, multicenter trial. A statistically significant improvement from baseline was observed within each treatment group (O4, O3A1, A4) in the evaluable population for all endpoints: WOMAC, Pain on Standing score, Investigator Global score, and Patient Global score (Table 2). Among treatment groups, clinical improvement was observed in patients in the evaluable population receiving the 3-injection (O3A1) and 4-injection (O4) Orthovisc® regimens compared to the control group. Due in part to the unexpectedly high response rate in the arthrocentesis (A4) group, statistically significant differences were only reported between the O4 and control (A4) groups for the Investigator Global score and Patient Global scores, based on the Hochberg procedure.

This study used arthrocentesis as the control group. This included aspirating the joint space to dryness, if fluid was present. Such aspiration may have removed degradative enzymes and catabolites involved in inflammation. This improvement may have contributed to the high placebo response observed in the arthrocentesis group. Such a strong placebo response has been reported by other investigators and is well documented[35,36]. Desmarais[37] showed that simply penetrating the knee joint with a needle without injection can decrease the degree of pain in some patients with OA. Similar results were reported by Cederlof and Jonson[38]. A similar placebo effect was reported when saline injection was used as the control[24].

All patients entering this study had failed the usual treatments for OA of the knee. The lack of response of the evaluable population was due in part to the inclusion of patients with K-L grade 1 in the evaluable population. Patients with K-L grade 1 do not have confirmed OA and should not have been included in this study. Such patients would not be candidates for treatment with Orthovisc®. For this reason, the K-L grade 1 patients were removed from the data set and the data were reevaluated using this evaluable subgroup. We believe the evaluable subgroup is the appropriate population for statistical analysis of the data.

Because of the high rate of response in the arthrocentesis control group, a significant number of control patients achieved the 20% improvement threshold established in the original statistical analysis plan. When 40% and 50% rates of improvement were assessed in the evaluable subgroup, further distinctions between O4 and A4 were revealed, demonstrating superiority of the 4-injection regimen to arthrocentesis (A4). This analysis showed greater improvement and to a larger degree (40% and 50%) in patients receiving the O4 regimen compared to the control group. Maximal improvement was observed at 8 weeks and persisted throughout this study (Weeks 8 to 22).

The control (A4) group did, however, show some improvement (20%). While a 20% improvement is clinically meaningful, 40% and 50% improvement are of much greater clinical significance, reflecting a much more desirable clinical outcome with even greater effect on the patient's quality of life. Further, 40% to 50% improvement as a clinical goal is a higher level of response than that observed in trials of naproxen for OA, where 30% improvement was seen[27].

The effectiveness of the 3-injection regimen was masked by the high rate of response in the arthrocentesis (control) group. A similar placebo effect was also observed in a previous study[24] with the 3-injection regimen of Orthovisc® using saline injections as the control. High placebo responses using arthrocentesis and saline injections as the control have been reported[24,35,37,38]. Brandt, *et al*[24] reported clinical improvement in WOMAC Pain score, Patient Global assessments, Investigator Global assessments, and Pain on Standing compared to saline (control) injections.

Our results indicate that Orthovisc® has an excellent safety profile, highlighted by a low rate of injection site reactions. There were no device-related serious adverse events, and device-related adverse events in general were < 9% in O4 and 5% in O3A1; there was no statistical difference among the O4, O3A1, and A4 groups in any of the adverse event comparisons analyzed. In contrast, trials of Synvisc reported severe acute pseudoseptic reactions[21-23]; no such reaction occurred with Orthovisc® in the present study.

The rate of injection site pain was 1.6% or less in O4 and O3A1 groups. In comparison, a trial of Hyalgan® reported a rate of 23% for injection site pain[27]. Overall injection site reactions were < 4% in the Orthovisc® groups in this and other studies[24]. Arthralgia was noted in 12.5% of O4 patients; however, only one case was deemed device-related. This rate is compared to the 17.8% rate reported with Supartz® [9]. In conclusion, Orthovisc® is extremely safe, with low incidences of device-related adverse reactions and a safety profile comparable to the other approved viscosupplementation devices.

In summary, our data demonstrate that high molecular weight hyaluronan (Orthovisc®) is a safe product for treatment of knee osteoarthritis. These data indicate that Orthovisc® seems to be effective in reducing the pain and symptoms associated with OA of the knee using a series of 3 or 4 injections. The potential benefit for clinically significant pain reduction using Orthovisc® outweighs the potential risk of a low rate of minor adverse effects.

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REFERENCES

1. Neustadt DH. Current approach to therapy for osteoarthritis of the knee. Louisville Med 2004;51:341-3.
2. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorder in the United States. Arthritis Rheum 1998;41:778-99.
3. Felts W, Yelin E. The economic impact of the rheumatic diseases in the United States. J Rheumatol 1989;16:867-884.
4. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendation for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;43:1905-15.
5. Laurent TC, Fraser JR. Hyaluronan. FASEB J 1992;6:2397-404.
6. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. Baillieres Clin Rheumatol 1997;11:769-94.
7. Anika Therapeutics, Inc. Orthovisc package insert. Woburn, MA: Anika Therapeutics; 2004.
8. Fidia Farmaceutici SpA. Hyalgan package insert. Abano Terme, Italy: Fidia Farmaceutici; 2001.
9. Seikagaku Corporation. Supartz package insert. Tokyo: Seikagaku Corp.; 2001.
10. Genzyme Corporation. Synvisc package insert. Cambridge, MA: Genzyme Corp.; 2004.
11. Neustadt DH. Intra-articular therapy. In: Howell DS, editor. Osteoarthritis. Diagnosis and medical/surgical management. 3rd ed. Philadelphia: WB Saunders Co.; 2001:407.
12. Ghosh P, Guidolin D. Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: Are the effects molecular weight dependent? Semin Arthritis Rheum 2002;32:10-37.
13. Forrester JV, Balazs EA. Inhibition of phagocytosis by high molecular weight hyaluronate. Immunology 1980;40:435-46.
14. Pisko E, Turner RA, Soderstrom LP, Panetti M. Inhibition of neutrophil phagocytosis and enzyme release by hyaluronic acid. Clin Exp Rheumatol 1983;1:41-4.
15. Hakansson L, Hallgren R, Verge P. Regulation of granulocyte function by hyaluronic acid. In vitro and in vivo effect on phagocytosis, locomotion and metabolism. J Clin Invest 1980;66:298-305.
16. Punzi L, Schiavon F, Cavasin F, Ramonda R, Aambari PF, Todesco S. The influence of intra-articular hyaluronic acid on PGE2 and cAMP of synovial fluid. Clin Exp Rheumatol 1989;7:247-50.
17. Sato H, Takahashi T, Ide H, et al. Antioxidant activity of synovial fluid, hyaluronic acid and two subcomponents of hyaluronic acid. Arthritis Rheum 1988;31:63-71.
18. Bernardeau C, Bucki B, Liote F. Acute arthritis after intra-articular hyaluronate injection: onset of effusions without crystal. Ann Rheum Dis 2001;60:518-20.
19. Martens PB. Bilateral symmetric inflammatory reaction to hylan G-F 20 injection. Arthritis Rheum 2001;44:978-9.
20. Goldberg VM, Coutts RD. Pseudoseptic reactions to hylan viscosupplementation: diagnosis and treatment. Clin Orthop 2004;419:130-7.
21. Puttick MP, Wade JP, Chalmers A, Connell DG, Rangno KK. Acute local reactions after intraarticular hylan for osteoarthritis of the knee. J Rheumatol 1995;22:1311-4.
22. Chen AL, Desai P, Adler EM, Di Cosare PE. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee: a report of six cases. J Bone Joint Surg Am 2002;84:1142-7.
23. Leopold SS, Warme WJ, Pettis PD, Shott S. Increased frequency of acute local reaction to intra-articular hylan GF-20 (Synvisc) in patients receiving more than one course of treatment. J Bone Joint Surg Am 2002;84:1619-23.
24. Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT, and the Orthovisc® Study Group. Efficacy and safety of intraarticular high molecular weight hyaluronan in knee osteoarthritis. Clin Orthop Rel Res 2001;385:130-43.
25. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomized placebo (saline) controlled clinical trial of 500-730 kDa high molecular weight hyaluronan (Hyalgan) on the radiological change in OA of the knee. Int J Clin Pract 2003;57:467-74.
26. Wang C-T, Lin J, Chang C-J, Lin Y-T, Hou S-M. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am 2004;86:538-45.
27. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan®) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group. J Rheumatol 1998;25:2203-12. Erratum in J Rheumatol 1999;26:1216.
28. Neustadt DH. Long-term efficacy and safety of intra-articular

sodium hyaluronate (Hyalgan) in patients with osteoarthritis of the knee. Clin Exp Rheumatol 2003;21:307-11.
29. Ranawat CS, Flynn WF Jr, Saddler S, Hansraj KK, Maynard MJ. Long-term results of the total condylar knee arthroplasty: a 15-year survivorship study. Clin Orthop 1993;278:94-102.
30. US Food and Drug Administration/Center for Devices and Radiological Health resources page. United States Food and Drug Administration Website. Available from: http://www.fda.gov/ Accessed March 25, 2005.
31. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. Ann Rheum Dis 1957;16:494-501.
32. Bellamy N. WOMAC Osteoarthritis Index: A user's guide. London, Canada: Victoria Hospital; 1995.
33. Armstrong CP, Blower AL. Non-steroidal anti-inflamatory drugs and life threatening complication of peptic ulceration. Gut 1987;28:527-32.
34. Towheed TE, Judd M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2003;(2):CD004257.
35. Friedman DM, Moore ME. The efficacy of intraarticular steroids in osteoarthritis: a double-blind study. J Rheumatol 1980;7:850-6.
36. Kirwan J. Is there a place for intra-articular hyaluronate in osteoarthritis of the knee? Knee 2001;8:93-101.
37. Desmarais MHL. Value of intraarticular injections in osteoarthritis: a controlled series. Ann Rheum Dis 1952;11:277-81.
38. Cederlof A, Jonson G. Intraarticular prednisolone injection for osteoarthritis of the knee: a double blind test with placebo. Acta Chir Scand 1966;132:532-6.