

A Prospective, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy of Intraarticular Hyaluronic Acid for Osteoarthritis of the Knee

ROBERT J. PETRELLA and MICHAEL PETRELLA

ABSTRACT. Objective. To assess the efficacy of intraarticular (IA) injections of hyaluronic acid (HA) compared to placebo in patients with osteoarthritis (OA) of the knee; and to assess patient satisfaction with treatment relative to placebo, and whether there is a difference between a series of 3 versus 6 consecutive IA injections.

Methods. We conducted a randomized, double-blind, placebo controlled, 2-arm parallel design trial of 106 patients with radiologically confirmed knee OA. Two-milliliter IA injections using 20 mg/ml HA sodium salt or saline placebo were administered once weekly over 3 weeks (HA and placebo groups), followed by once weekly IA injection with 2.0 ml (20 mg/ml) HA for a further 3 consecutive weeks. The primary efficacy assessment included Western Ontario and McMaster Universities osteoarthritis index (WOMAC) score for knee pain (Week 3 score). Secondary efficacy assessments included WOMAC scores for knee pain at Weeks 6 and 12 (followup), as well as WOMAC stiffness, physical function and quality of life scores, visual analog scale (VAS) scores for pain at rest and following walking and stepping activity, range of knee joint motion, and global patient satisfaction with treatment and quality of life using the SF-36.

Results. After 3 weeks of study treatment, both treatment groups showed improvements in knee function, the HA group showing a greater improvement compared to placebo in WOMAC knee pain score ($p < 0.01$). The HA group showed greater ($p < 0.05$) improvement in the overall WOMAC score and VAS pain following walking and stepping activity at Week 3. Results from all other secondary efficacy assessments at Weeks 6 and 12 including patient satisfaction were similar and were not statistically significant between treatment groups, and there were no significant differences between groups for adverse events.

Conclusion. Intraarticular HA was superior to placebo in improving knee pain and function, with no difference between 3 or 6 consecutive injections for the primary efficacy assessment. (J Rheumatol 2006;33:951-6)

Key Indexing Terms:

HYALURONIC ACID OSTEOARTHRITIS DOSING FREQUENCY KNEE

Recent studies have shown that intraarticular (IA) hyaluronic acid (HA) injections into osteoarthritic (OA) knees are well tolerated, resulting in improved pain control and function similar to conventional therapeutic options¹⁻⁶. However, the magnitude of this effect may be influenced by issues of experimental and methodological design including small sample

sizes, types of outcomes measures and entry criteria used, duration of observation, inclusion of comparators, choice of HA with differing rheological characteristics (molecular weight and concentration), and dosing schedule⁷⁻⁹. In particular, HA dosing has differed in various regions of the world, primarily between 3 and 6 weekly injections, without a specific rationale for the choice^{7,10}.

We have previously reported the benefit of 3 weekly injections of HA 20 mg/ml in a randomized clinical trial³ compared to placebo and conventional therapy, and more recently in a longterm experience in clinical practice⁵.

This randomized, placebo controlled trial was designed to evaluate the efficacy of IA HA in patients with OA of the knee, and specifically to determine whether there is a difference between 3 versus 6 consecutive weekly injections in terms of pain and functional outcomes and patient satisfaction/quality of life.

From the Departments of Family Medicine and Physical Medicine and Rehabilitation, Schulich School of Medicine and School of Kinesiology, Faculty of Health Sciences, The University of Western Ontario, London, Ontario, Canada.

Supported by a grant from Bioniche Life Sciences, Belleville, Ontario, Canada. R.J. Petrella is supported by a Canadian Institutes of Health Research Investigator Award in Healthy Aging.

R.J. Petrella, MD, PhD; M. Petrella, PhD.

Address reprint requests to Dr. R.J. Petrella, Heart Health and Exercise Laboratory, 1490 Richmond Street, London, Ontario N6G 2M3.

E-mail: petrella@uwo.ca

Accepted for publication December 13, 2005.

MATERIALS AND METHODS

Study design. A placebo controlled, randomized, double-blind, parallel group design was utilized for this clinical trial to evaluate the efficacy of IA HA compared to placebo in patients with radiographically confirmed knee OA. The trial had 3 parts: the double-blind treatment phase (Weeks 1 to 3), the extended treatment phase (Weeks 4 to 6), and followup Week 12 (Figure 1). A total of 106 patients, 53 per treatment group with OA of the knee, were randomized to receive either 20 mg/ml, 2.0 ml HA sodium salt or 2.0 ml saline placebo IA injections once weekly for 3 weeks in the first double-blind treatment phase. Following the third injection, all patients received 3 additional weekly injections of HA in the second, extended double-blind treatment phase. Patients returned to the clinic for a followup visit at Week 12.

The study design was deemed appropriate for determining the effective-

ness of HA compared to placebo and comparing the treatment regimens of a 3-weekly injection phase versus a 6-week injection phase. The efficacy of HA was assessed using outcomes suggested for OA studies of pain, stiffness, function and quality of life^{11,12} including Western Ontario and McMaster Universities (WOMAC)¹³ OA index for knee and hip OA, visual analog scale (VAS) scores for pain assessment at rest and during standardized walking and stepping activity³, range of motion assessment, and patient global satisfaction with treatment and quality of life using the Medical Outcomes Study Short Form-36 Health Survey (SF-36)¹⁴. Efficacy assessments were performed prior to the first administration of study treatment at each weekly visit by a blinded research assistant.

Study population. Patients were over age 18 years, and all provided informed consent. All patients had radiographically diagnosed knee OA between grades

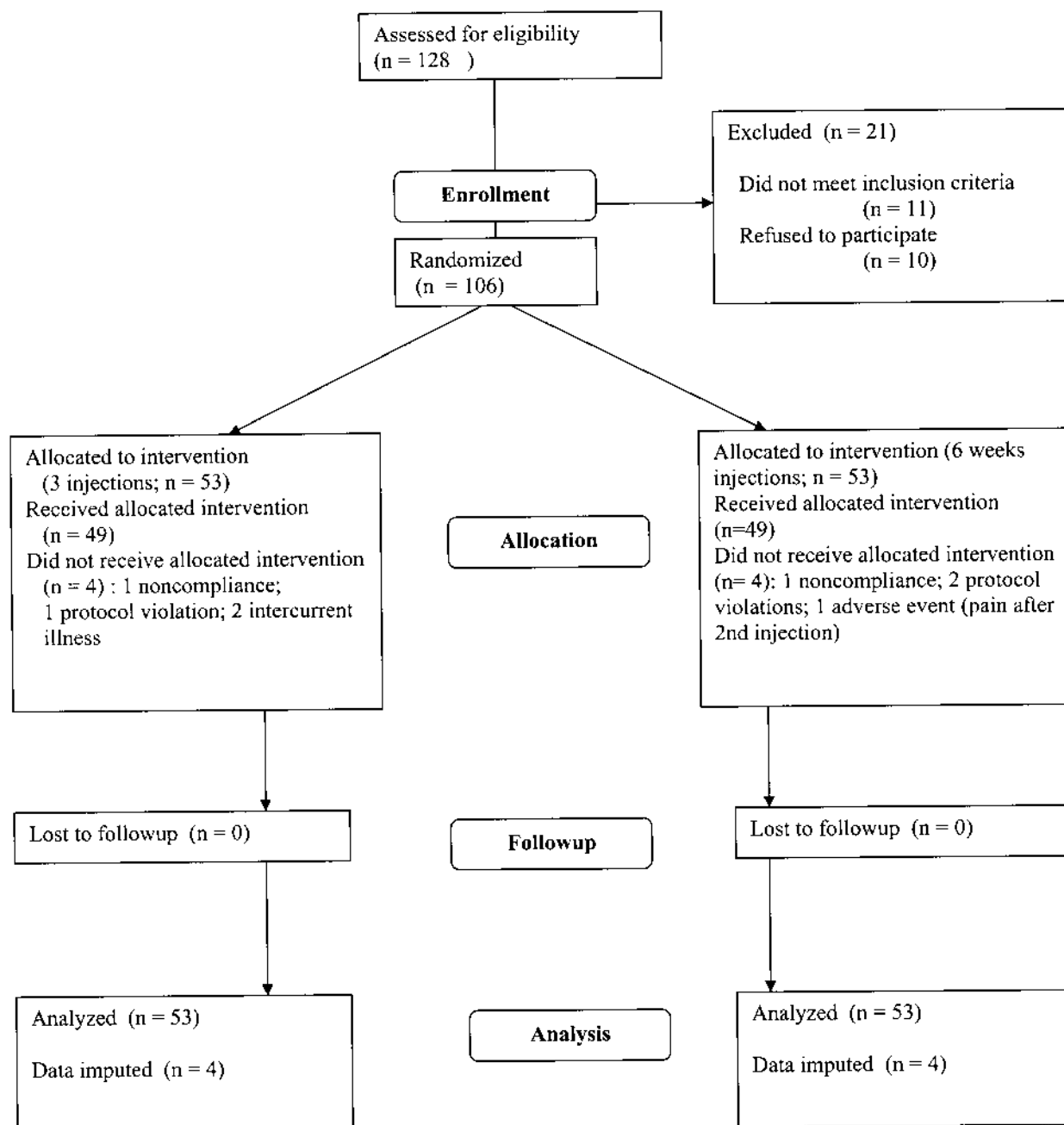


Figure 1. Disposition of subjects during the study protocol.

1 and 3¹⁵. All patients were also required to have resting pain VAS score > 45 cm in one knee. That knee was considered the index knee for all further assessment and treatment. Exclusion criteria included non-OA conditions of the knee, contraindication to HA injection, current or prior IA therapies in the last 6 months, and current use of oral corticosteroids or nonsteroidal anti-inflammatory medications (NSAID). Acetylsalicylic acid < 325 mg daily was permitted for cardiovascular prophylaxis and acetaminophen < 500 mg daily was permitted as rescue analgesia. The study was approved by the institutional review board of the University of Western Ontario.

Study treatments. Study treatments were supplied by the sponsor of the trial to the investigator site in sealed packages with blinded syringes. Study medication included a 20 mg/ml dose of HA sodium salt, which was selected because it is a current standard of therapy in Canada and Europe, where the dosing interval ranges from 3 to 6 consecutive injections. Each syringe contained 2 ml per volume of HA or saline placebo. All patients received injections through a 23 gauge 1.5 inch needle administered by the blinded study physician. No anesthetic was used. Patients were randomized according to a computer generated randomization code. Treatment was assigned sequentially by an investigator-designee using the lowest randomization number available. Double-blinding was achieved by the identical appearance and design of the syringes.

The schedule of study procedures and assessments is shown in Table 1.

Efficacy assessments

Primary efficacy assessment. The WOMAC is a multidimensional self-administered outcome measure developed for clinical trials in patients with hip and knee OA¹³ and is recommended by the conjoint OMERACT and CONSORT^{11,12}. The WOMAC used in this study consisted of 25 items grouped into 3 domains; pain (6 questions), stiffness (2 questions), and physical function (17 questions). Each item is scored on a zero to 10 centimeter VAS.

Secondary efficacy assessments. Patients were asked to assess pain related to their knee OA at the following times: after 5 minutes of seated rest, immediately following a self-paced walk of 2 circuits of 20 m, and after another 5 minute rest, 20 circuits of a 2 steps measuring 9 cm each³. Pain was scored using a 0–10 cm VAS.

Other secondary efficacy outcomes included range of motion assessment using a standard goniometer, patient global satisfaction assessment including a 5 point categorical scale⁵, and quality of life overall and with subscales using the SF-36¹⁴. Radiographs were assessed by a blinded observer¹⁵.

Data management. All clinical data were entered into Oracle Clinical (v. 7.3.3.6.0) database via double data entry. The data were then exported and analyzed using SAS (v. 6.12).

Statistical analysis. The null hypothesis was that no difference in WOMAC overall knee pain at Week 3 relative to baseline between treatment and placebo groups would be observed. A total of 84 evaluable patients, 42 per treatment arm, were required to complete all measurements ($\alpha = 0.05$; $\beta = 0.20$).

Patients were included if they had all baseline efficacy assessments and received at least one post-randomization injection during the first double-blind treatment phase. An intent-to-treat analysis was performed where the method of last observer carried forward was used to impute missing data.

The continued efficacy of HA 3 versus 6 injections was assessed using Week 6 and Week 12 data. Patients who provided data at baseline and at Week 6 were included in this population as appropriate with no imputation of missing data.

Summary statistics were provided for patient demographics collected at the baseline visit. In addition, summary statistics were also tabulated for the following baseline assessments: overall WOMAC score, as well as WOMAC score for complaints of stiffness, pain, and physical function; pain assessment VAS scores; patient global satisfaction with treatment; range of knee joint motion; and SF-36 quality of life. Medications taken prior to the first administration of study injection treatment (concomitant medication) were summarized by treatment group as appropriate.

Efficacy variables. ANOVA models were used to assess the change from baseline to Weeks 3, 6, and 12 for each of the primary and secondary efficacy assessments between treatment groups. Analysis of the pain assessment VAS scores was conducted through tabulation of summary statistics. Summary statistics were tabulated for each subgroup VAS score (e.g., rest prior to activity, walking, step test, and rest following activity).

Assessment of patient satisfaction between the treatment groups was performed using shift tables, documenting change in response from baseline to Weeks 3, 6, and 12, respectively, and ANOVA techniques to assess treatment effects. Calculation of individual SF-36 component scores was tabulated for each of the SF-36 domains, and ANOVA was used to assess the treatment effect on the change from baseline to Weeks 3, 6, and 12 for each of the domains.

Primary and secondary efficacy assessments were also examined at Week 12 to assess the effect of discontinuation of therapy as well as treatment status relative to baseline. Comparisons between patients originally randomized to HA and patients originally randomized to placebo were conducted. Data

Table 1. Schedule of assessments. All procedures at Visit 1, except for adverse event assessment, were performed prior to administration of the study treatment. All pretherapy assessments conducted at Visit 1 were considered to be the baseline data.

	Visit 1, Week 1	Visit 2, Week 2	Visit 3, Week 3	Visit 4, Week 4	Visit 5, Week 5	Visit 6, Week 6	Visit 7, Week 12 Followup
Informed consent	•						
Inclusion/exclusion	•						
Medical history	•						
Clinical examination	•						
Study treatment	•	•	•	•	•	•	
WOMAC	•	•	•	•	•	•	•
VAS—rest pain assessment	•	•	•	•	•	•	•
VAS—walking and stepping activity pain	•	•	•	•	•	•	•
Range of motion	•	•	•	•	•	•	•
Patient global assessment	•	•	•	•	•	•	•
SF-36	•	•	•	•	•	•	•
Adverse event reporting	•	•	•	•	•	•	•
Concomitant medication reporting	•	•	•	•	•	•	•

were analyzed independently by the University of Western Ontario Biostatistical Support Unit.

RESULTS

Study population and baseline comparability. As shown in Figure 1, 21 of 128 (16.4%) patients screened did not meet entry criteria. The primary reasons for exclusion were withdrawal of consent and inability to tolerate discontinuation of OA medications. The proportion of patients who completed the study was similar between treatment groups. Four patients in each group discontinued prematurely. Distribution of study patients and the analysis data set was similar between treatment groups.

Demographic characteristics. There were no statistically significant differences between treatment groups with respect to demographic characteristics at baseline (Table 2). The distribution of men and women was similar between groups (53.7% male for placebo, 56.9% male in the HA group). The mean age was 62.4 years (range 38–85) in patients receiving placebo and 63.9 years (range 40–83) in patients receiving HA. The mean weight and height was 87.4 kg and 167.8 cm for the placebo group and 85.7 kg and 169.3 cm for the HA group. The radiographic grade of OA of the knee was similar between both groups, most having grade 2. Prior medication use among groups was similar, 92.6% of placebo and 92.5% of HA patients having taken NSAID prior to enrolment.

Primary efficacy analyses. At baseline, the WOMAC scores for knee pain were similar between HA and placebo groups, 20.0 ± 12.1 versus 20.6 ± 12.3 , respectively. At Week 3, both groups showed a significant improvement ($p < 0.05$) in mean

scores from baseline; however, patients who received HA showed a significantly greater improvement (mean change 8.0 ± 9.9) compared to placebo (mean change 2.8 ± 7.9 ; $p < 0.02$). Significant ($p < 0.05$) improvements in WOMAC pain, stiffness, physical function, and quality of life scores were observed at Week 3 in the HA group compared to placebo, while no further difference was observed between groups at Weeks 6 or 12.

Secondary efficacy analyses. At baseline, the treatment groups showed similar improvement in secondary efficacy assessments at Week 3. These included VAS pain assessment at rest and following activity, range of motion, patient global satisfaction with OA treatment, and quality of life (Table 3). No significant differences at Week 6 or 12 were observed between groups for any of the secondary efficacy assessments, save for significantly improved SF-36 vitality and physical function scores at Week 12 (Table 3).

The HA group was improved in global patient satisfaction with OA treatment and WOMAC quality of life score from baseline at Weeks 3, 6, and 12, while the placebo group improved at Weeks 6 and 12 (Table 3).

In all 3 phases of the study, adverse symptoms were reported as mild in severity and consisted of those similar to pre-morbid symptoms including pain and swelling. There were no deaths or severe adverse events reported in this study. The frequency of study discontinuation due to adverse events was low, occurring in one placebo and 2 HA patients.

DISCUSSION

After 3 weeks of study treatment, patients who received HA had greater improvement in knee pain and function than placebo patients. This was coincident with improved patient satisfaction. A placebo effect was observed at Week 3, which is consistent with previous reports, where injection expectation may lead to perceived benefit^{7,16}. Further, an 8 mm difference in pain using objective measurement is considered a clinically significant reduction in pain. However, the treatment effect with HA was still significantly greater than the placebo effect, and both groups showed significantly greater than baseline effect at Weeks 6 and 12. Importantly, HA treatment was highly satisfactory and was associated with few adverse events, while no further difference was observed between groups after 3 or 6 HA injections, and the benefits were unchanged at 12 weeks.

Hence this randomized, double-blind, placebo controlled study confirmed previous reports¹⁻⁶ that HA was superior to placebo IA injection for OA of the knee, and resulted in few adverse events, and no difference was observed whether 3 or 6 consecutive injections were delivered.

Clinical trial evidence for HA in the treatment of OA to date has been limited by a paucity of studies over 12 weeks' duration, or studies in which multiple treatment cycles have been included⁷. In a recent report, we described the effect of HA over 7 years in a longterm naturalistic setting⁵. Not only

Table 2. Demographic characteristics at baseline in the intent-to-treat population.

	Placebo	HA
Sex, N (%) a		
Male	29 (53.7)	29 (56.9)
Female	25 (46.3)	22 (43.1)
Age, yrs, N	54	51
Mean (SD)	62.4 (10.3)	63.9 (9.3)
Minimum	38	40
Maximum	85	83
Weight, kg		
N	54	50
Mean (SD)	87.4 (14.8)	85.7 (16.4)
Minimum	49.8	57.0
Maximum	124.5	122.0
Height, cm		
N	54	50
Mean (SD)	167.8 (8.6)	169.3 (10.0)
Minimum	149.0	150.0
Maximum	185.0	191.5
OA grade, N (%)		
1	8 (14.8)	5 (9.8)
2	30 (55.6)	35 (68.6)
3	16 (29.6)	11 (21.6)
4	0	0

Table 3. Mean change from baseline/Week 6 in primary and secondary efficacy pain and function assessments at Week 6 and 12 (followup) in the extended treatment and followup populations.

	Placebo	HA	p
WOMAC—knee pain			
Mean change from baseline at Week 6 (SD)	-8.1 (10.0)*	-8.0 (11.6)	0.94
Mean change from Week 6 at followup (SD)	-2.5 (5.4)	-2.2 (4.8)	0.84
WOMAC—stiffness			
Mean change from baseline at Week 6 (SD)	-4.2 (4.3)*	-5.2 (4.8)	0.28
Mean change from Week 6 at followup (SD)	-1.0 (2.5)	-0.7 (2.7)	0.62
WOMAC—physical function			
Mean change from baseline at Week 6 (SD)	-27.0 (27.8)*	-22.9 (28.0)	0.49
Mean change from Week 6 at followup (SD)	-5.1 (15.9)	-4.8 (14.9)	0.93
Pain assessment (VAS)—walking			
Mean change from baseline at Week 6 (SD)	-3.6 (2.1)*	-3.6 (2.0)	0.91
Mean change from Week 6 at followup (SD)	-0.3 (1.7)	-0.2 (1.0)	0.82
Pain assessment (VAS)—stepping			
Mean change from baseline at Week 6 (SD)	-1.5 (2.6)	-1.6 (2.4)	0.90
Mean change from Week 6 at followup (SD)	-0.3 (1.8)	-0.2 (1.2)	0.89
ROM—flexion			
Mean change from baseline at Week 6 (SD)	5.9 (13.2)*	5.6 (10.8)	0.89
Mean change from Week 6 at followup (SD)	2.0 (11.9)	0.8 (10.8)	0.59
Patient global assessment—knee condition			
Mean change from baseline at Week 6 (SD)	-4.5 (0.8)	-3.4 (0.9)	0.35
Mean change from Week 6 at followup (SD)	0.0 (0.7)	-0.2 (0.7)	0.19
SF-36—physical function			
Mean change from baseline at Week 6 (SD)	1.0 (3.3)	1.3 (3.8)	0.70
Mean change from Week 6 at followup (SD)	1.5 (2.7)*	3.2 (2.5)†	0.55
SF-36—vitality			
Mean change from baseline at Week 6 (SD)	1.0 (3.3)	0.8 (2.4)	0.72
Mean change from Week 6 at followup (SD)	2.1 (2.1)*	2.6 (1.4)†	0.08

p value is comparison between groups, * p < 0.05 within groups vs Week 3. † p < 0.001. WOMAC: Western Ontario McMaster Universities OA index score; ROM: range of knee joint motion in degrees.

did symptoms improve up to 26 weeks after a course of 3 weekly HA injections, this was also progressively greater with successive treatment cycles. In the current study, we have provided further information regarding optimal HA treatment for OA. In particular, it has been unclear whether repeated IA series or differing number of injections per cycle would have further improved symptom control or whether this would be associated with a change in adverse event rates.

The American College of Rheumatology¹⁷ has previously stated that "...while clinical trials of intra-articular hyaluronan preparations appear to improve pain relief comparable to oral anti-inflammatory preparations, these trials have been limited in the duration of observation, as well as experience with effectiveness of multiple courses of intra-articular hyaluronan therapy". Hence our study provides important evidence for the efficacy of HA in the treatment of OA of the knee and that this is optimal using current treatment cycle of 3 consecutive IA injections. While no further improvement was observed with increasing the injection cycle to 6 consecutive HA injections for most efficacy assessments, we did observe a significant improvement in the vitality and physical function subscales of the SF-36 at Week 12 in the HA group. Further studies should explore whether these changes may support the role of con-

tinued HA injections on more global functional outcomes beyond simple pain and functional activity, as assessed in this study.

Strengths of the study included the use of a predefined pain threshold for inclusion, and use of a randomized, double-blind design, with a placebo comparison group and crossover of placebo group to active treatment. Further strengths included our use of outcomes measures consistent with those recommended in the literature^{11,12} and the fact that we directly addressed a gap in current HA knowledge as described in the literature^{7-9,17}. A limitation of this study includes the absence of a control group. While we observed a significant improvement in primary and secondary efficacy assessments in the placebo group at 3 weeks, this is consistent with results observed in the literature of as high as 80%⁷. We utilized a widely available HA product with standard dosing as described in North America and Europe, and hence the results can be generalized to those who receive HA in the general population. However, it is possible that alternative dosing regimens, perhaps utilizing alternative molecular weight or concentration of HA, could influence these findings (including longer duration of effects) and require future investigation.

REFERENCES

1. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. *Arthritis Rheum* 1994;37:521-8.
2. Dougados M, Nguyen M, Lustrat V, Amor B. High molecular weight sodium hyaluronate (hyalectin) in osteoarthritis of the knee: a 1-year placebo-controlled trial. *Osteoarthritis Cartilage* 1993;1:97-103.
3. Petrella RJ, DiSilvestro MD, Hildebrand C. Effects of hyaluronate sodium on pain and physical functioning in osteoarthritis of the knee. *Arch Intern Med* 2002;162:292-8.
4. Karlsson J, Sjogren LS, Lohmander LS. Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis: a controlled, randomized, double-blind, parallel-design multi-center study. *Rheumatology Oxford* 2002;41:1240-8.
5. Petrella RJ. Hyaluronic acid for the treatment of knee osteoarthritis: Long-term outcomes from a naturalistic primary care experience. *Am J Phys Med* 2005;84:278-83.
6. Lussier A, Cividino AA, McFarlane CA, Olszinski WP, Potashner WJ, DeMedicis R. Viscosupplementation with hyalgan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol* 1996;23:1579-85.
7. Lo GH, LaValley M, McAlindon T, Felson DT. Intraarticular hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003;290:3115-21.
8. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2005;2:CD005321.
9. Arrich J, Prirbauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta analysis. *CMAJ* 2005;172:1039-43.
10. Balasz EA, Denlinger SL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol* 1993;20 Suppl 39:3-9.
11. Bellamy N. Osteoarthritis clinical trials: Candidate variables and clinimetric properties. *J Rheumatol* 1997;24:768-78.
12. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting clinical trials: The CONSORT statement. *JAMA* 1996;276:637-9.
13. Bellamy N, Buchanan W, Goldsmith C, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.
14. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36. Health survey manual and interpretation guide. Boston: New England Medical Centre, The Health Institute; 1993.
15. Altman RD, Fries JF, Bloch DA, et al. Radiographic assessment of progression in osteoarthritis. *Arthritis Rheum* 1987;30:1214-25.
16. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan GF-20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multi-centre trial comparing hylan GF-20 alone, hylan GF-20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage* 1995;3:213-26.
17. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905-15.