

# A Double Blind, Randomized, Multicenter, Parallel Group Study of the Effectiveness and Tolerance of Intraarticular Hyaluronan in Osteoarthritis of the Knee

RICHARD DAY, PETER BROOKS, PHILIP G. CONAGHAN, and MARISA PETERSEN for the Multicenter Trial Group

**ABSTRACT. Objective.** To investigate the efficacy and tolerability of a course of 5 injections of hyaluronan (HA) given at intervals of one week in patients with symptomatic, mild to moderate osteoarthritis (OA) of the knee.

**Methods.** A double blind, randomized, parallel group, multicenter (17 centers), saline vehicle-controlled study was conducted over 18 weeks. Patients received either 25 mg (2.5 ml) HA in a phosphate buffered solution or 2.5 ml vehicle containing only the buffer by intraarticular injection. Five injections were given at one week intervals and the patients were followed for a further 13 weeks. The Western Ontario McMaster (WOMAC) OA instrument was used as the primary efficacy variable and repeated measures analysis of covariance was used to compare the 2 treatments over Weeks 6, 10, 14, and 18.

**Results.** Of 240 patients randomized for inclusion in the study, 223 were evaluable for the modified intention to treat analysis. The active treatment and control groups were comparable for demographic details, OA history, and previous treatments. Scores for the pain and stiffness subscales of the WOMAC were modestly but significantly lower in the HA-treated group overall (Weeks 6 to 18;  $p < 0.05$ ) and the statistically significant difference from the control was not apparent until after the series of injections was complete. The physical function subscale did not reach statistical significance ( $p = 0.064$ ). Tolerability of the procedure was good and there were no serious adverse events that were considered to have a possible causal relationship with the study treatment.

**Conclusion.** Intraarticular HA treatment was significantly more effective than saline vehicle in mild to moderate OA of the knee for the 13 week postinjection period of the study. (J Rheumatol 2004;31:775–82)

**Key Indexing Terms:**

OSTEOARTHRITIS  
VISCOSUPPLEMENTATION

HYALURONAN

INTRAARTICULAR THERAPY  
KNEE OSTEOARTHRITIS

Osteoarthritis (OA) of the knee is a common disorder, particularly in the elderly, and is associated with a large economic burden<sup>1</sup>. Management options to reduce pain and improve joint function include the use of simple analgesics, notably acetaminophen, nonsteroidal antiinflammatory drugs (NSAID), intraarticular (IA) corticosteroid injections, joint replacement, and various physical approaches including quadriceps muscle strengthening exercises<sup>2,3</sup>. Another therapeutic approach involves the injection of

hyaluronan (HA, formerly called hyaluronic acid) into the knee.

HA is a polysaccharide molecule synthesized by most mammalian cells and is a major component of both the synovial and cartilage extracellular matrix. At a molecular level, HA influences tissue hydration, interacts with other extracellular macromolecules, and interacts with cell receptors, especially CD44<sup>4</sup>. Synovial lining cells are the major source in the synovium and HA forms the major nonprotein component of synovial fluid (SF). The HA content of SF determines its viscosity and thus its lubricating properties in relation to articular cartilage. In OA, HA molecular weight and concentration are reduced<sup>5</sup> and the viscosity of SF decreases due to the depolymerization, leading to impaired lubrication<sup>6</sup>.

These types of data led to the concept of viscosupplementation therapy, achieved by injection of HA into synovial joints in order to restore viscosity and elasticity of the SF<sup>7</sup>. Results from use of HA in animal models of arthritis were encouraging and supported this concept<sup>8</sup>. Despite the development and licensing of a number of HA products for use in human OA and their place in therapeutic

*From the Department of Clinical Pharmacology and Toxicology, University of New South Wales, Sydney, Australia.*

*Supported by the Seikagaku Corporation, Tokyo, Japan.*

*R. Day, MD, FRACP, Professor of Clinical Pharmacology, University of New South Wales, St. Vincent's Hospital, Sydney; P. Brooks, MD, FRACP, Executive Dean, Health Sciences, University of Queensland, Herston, Queensland, St. Vincent's Hospital; P.G. Conaghan, MB, BS, FRACP, St. Vincent's Hospital (present address: Academic Unit of Musculoskeletal and Rehabilitation Medicine, University of Leeds, Leeds, UK); M. Petersen, PhD, Omnicare Clinical Research, North Ryde, Australia.*

*Address reprint requests to Dr. R. Day, Department of Clinical Pharmacology and Toxicology, University of New South Wales, St. Vincent's Hospital, Victoria Street, Darlinghurst, Sydney 2010 Australia. E-mail: R.Day@unsw.edu.au*

*Submitted October 7, 2002; revision accepted September 3, 2003.*

recommendations<sup>2,3</sup>, controversy still exists over the efficacy of these agents.

There are 2 main reasons for this controversy. First, the results from randomized clinical trials in human OA using different HA have shown variable outcomes<sup>9-24</sup>. Problems with the design of HA studies have been reviewed<sup>25-27</sup>. Recently, Felson and Anderson have presented a review of the few large, randomized HA studies reported to date<sup>28</sup>. They demonstrated that there was no benefit for HA in these studies compared to placebo when examined by intention to treat (ITT) analysis. Second, despite much scientific work, the mechanism of action for HA in humans remains unclear. Efficacy of HA has been reported for up to 6 months and longer after completion of a course of injections, well after the introduced HA has been cleared from the joint into which it was injected. A combination of direct effects resulting from restoration of rheological properties of SF and indirect effects perhaps related to suppression of inflammation and pain or to effects on the cartilage itself encompass current views concerning the actions of IA HA<sup>27</sup>. A recent synovial biopsy study as part of an IA HA trial in OA suggested a direct antiinflammatory effect of HA<sup>29</sup>. However, Brandt, *et al* recently reviewed the mechanism of action literature and found no compelling data to support any of the hypothesized actions<sup>27</sup>. We evaluated the efficacy and safety of IA HA in patients with OA of the knee using the WOMAC instrument<sup>30</sup> as the primary outcome measure.

## MATERIALS AND METHODS

**Study design.** This was a prospective, randomised, multicenter, double blind (blind observer and patient technique) study. Patients were randomized using a random number generator and block randomization to 2 parallel groups, one receiving IA injections of 1% sodium HA and the other receiving IA injections of vehicle. The 2 experimental preparations were visually distinguished only by their different viscosities, therefore double blind conditions were maintained by having the injections performed by a physician other than the "observing" physician. The observing physician and the patient had no access to the trial preparations and remained blinded.

The study was carried out at 17 investigational centers throughout Australia: Queensland (n = 3), New South Wales (5), Victoria (6), South Australia (2), and Western Australia (1). The contract research organization Omnicare Clinical Research, North Ryde, Australia, was responsible for the management, monitoring and safety reporting of the study.

The test medications were provided by Seikagaku Corporation, Tokyo, Japan. Each ampoule of the active medication contained 25 mg of sodium HA in 2.5 ml of phosphate buffered saline (ARTZ<sup>TM</sup>; batch no. C4F27S). The sodium HA was extracted from rooster combs and the purified material has a molecular weight of  $6.2 \times 10^5$  to  $11.7 \times 10^5$  Da. Each ampoule of the control solution contained 2.5 ml of the PBS vehicle (batch no. C4F28S). The test preparations were injected into the knee joint cavity at a dose of one ampoule per week for a total of 5 weeks (study weeks 1-5).

The duration of the study was 18 weeks, comprising a one week run-in phase, a 4 week treatment phase (5 injections, each one week apart), and a 13 week followup phase. Patients visited the clinic at weekly intervals for the first 6 weeks, then every 4 weeks until study completion. At Visit 1, patients' eligibility for the study was confirmed by review of history, clinical examination, and radiograph of the knee to be treated. They then were entered into the run-in phase (one week). Blood was taken for baseline

hematology and clinical chemistry assessments. All OA medications and physical therapy regimens were stopped. Patients were provided with instruction on a set of standard physiotherapy exercises to be performed throughout the study and with acetaminophen packed and labeled for the study, to be used only for additional relief of pain in the knee to be treated. Patients were instructed in the daily use of a diary card on which was recorded compliance with standard physiotherapy and the use of any additional analgesia (acetaminophen). Patients were also asked to record adverse events and changes in concomitant medications. Adverse events were defined as any unwanted event occurring during the course of the trial whether it was considered to be related to administration of the study drug or not. At each subsequent visit efficacy evaluations were conducted and adverse events and concomitant medications were recorded prior to administration of study medication. Where possible, evaluations for an individual were performed at the same time each visit. Patients were instructed not to take analgesics if possible on assessment days. Diary cards were reviewed, returned acetaminophen was counted, and new supplies were provided at each visit. One week after the completion of the treatment, blood was taken for hematology and clinical chemistry evaluations, and during the followup phase, global assessments of the condition of the knee were made by both the observing physician and the patient.

**Injection technique.** At each site the investigator was assisted by an "injecting physician" who by necessity was unblinded to treatment. This physician took no part in the assessment of patients in the study. Local anesthesia was achieved using 1% lignocaine solution infiltrated percutaneously and down to, but not through, the joint capsule. Before injection of the drug, any effusion of the knee joint was aspirated using a 21 gauge needle, and the volume noted. After aspiration of the joint, the trial solution was administered using the same 21 gauge needle for injection. Either the lateral or medial approach for injection could be used at the discretion of the injector; however, the same approach was to be used for all injections to one patient. The patient was unable to observe the injection process by means of a shield placed at about the mid-abdomen level.

Approval for the study was obtained under the Clinical Trial Notification Scheme of the Therapeutic Goods Administration, Department of Health, Australia. The study was reviewed and approved by the institutional ethics committees associated with each study center prior to commencement of the study. The study was performed in accord with the revised Declaration of Helsinki, 1989, the National Health and Medical Research Council Statement on Human Experimentation including Supplementary Notes, 1987 (Australia), and the Australian Code of Good Clinical Research Practice 1991.

**Patient study population.** Patients with the following 5 characteristics were eligible: (1) men and women aged between 40 and 75 years inclusive with a body mass index < 40. Pregnant and lactating women were excluded from the study and appropriate contraceptive measures for fertile patients were required. (2) Patients with a diagnosis of mild to moderate, idiopathic, painful femorotibial OA of the knee as defined by: (i) knee pain while standing, walking, and/or in motion, of at least 3 month duration, and (ii) evidence of femorotibial osteophytes and/or joint space narrowing based on standing (extended knee) anteroposterior and lateral knee radiographs taken during the previous 6 months.

Complete loss of joint space was an exclusion criterion. Predominant patellofemoral OA as the primary diagnosis on clinical and radiographic grounds was an exclusion criterion. Patients with severe malalignment of the knee or a large, tight effusion were excluded. Patients with clinical manifestations of OA of the hip and/or history of a joint replacement in the lower extremities, a history of surgery on the knee within the previous 12 months, or arthroscopy within the previous 6 months were excluded. Patients with other arthritides such as inflammatory arthritis or gout were excluded. (3) Patients with unilateral or predominantly unilateral symptomatology. (4) Patients who gave their informed written consent to participate. (5) Patients willing to discontinue their current OA treatment for the study duration (18 weeks), starting one week prior to their first injection.

This included treatment with any IA injections, oral corticosteroids, NSAID, nutraceuticals, complementary and herbal therapies, occlusive dressings, physiotherapy (other than that sanctioned for the study), or orthopedic devices. Patients with a history of any IA injection of corticosteroid or HA in the previous 3 months were excluded.

**Evaluation of efficacy and safety.** The WOMAC Osteoarthritis Scale of the patient's assessment of their pain, stiffness, and physical function was used as the primary efficacy measure<sup>30</sup>. Secondary criteria for evaluation included the Lequesne Index of severity of knee symptoms<sup>31</sup> (included because it was validated and chosen as the primary efficacy measure in a number of European countries), knee examination (4 point categorical scales for grading pain at rest, pain on movement, crepitation and effusion; knee flexion and extension using goniometry), physician and patient global assessments, and acetaminophen consumption. The occurrence of systemic and local adverse events, defined as any unwanted event whether it was thought to be related to the study drugs or not, was recorded, and clinically significant changes in laboratory variables were documented.

**Statistics.** Statistical analysis was carried out independently by Dr P. McCloud and associates of University Statistical Consulting Group, Monash University, Clayton, Victoria, Australia. The aim of the study was to test the null hypothesis that there was no difference between the HA and vehicle solution treatment groups at a significance level of  $p < 0.05$  and with statistical power of 90% to detect a prespecified, clinically significant difference in the primary efficacy measure. A reduction of 10% in WOMAC pain score was considered to be clinically significant<sup>32,33</sup>. The sample size calculations indicated that 200 patients would be sufficient to detect this difference. Two hundred forty patients were enrolled to allow for dropouts.

For efficacy analyses, 2 study populations were defined prior to breaking the treatment code: (1) Modified Intention to Treat (mITT) population — all subjects who received a dose of study medication and had at least one efficacy observation recorded after treatment; and (2) Per Protocol (PP) population — all subjects who received at least 3 injections of study medication and did not have significant protocol deviations as determined by the principal investigators (RD and PB).

For the primary analysis, the means of the WOMAC scores were compared between the 2 treatment groups on an mITT basis. Scores recorded at Weeks 6, 10, 14, and 18 were evaluated. Patients who were withdrawn prior to the end of the study were included in the analysis using the "last observation carried forward" technique. Only the mITT results are presented as the PP analysis was identical (208 patients).

Repeated measures analysis of covariance (ANCOVA) was carried out to consider the difference between the treatment groups in the WOMAC and Lequesne scores recorded at Weeks 6, 10, 14, and 18. The ANCOVA model included factors for treatment, center, and visit number and considered the possibility of "treatment by center" and "treatment by visit" interactions. The baseline score was used as the covariate.

## RESULTS

Of 240 patients who met criteria for inclusion into the study and were randomized to HA or control treatments, 223 were valid for mITT analysis (see modified CONSORT flow-chart, Figure 1). Of the 223 mITT patients, 108 had been randomized to HA and 115 to vehicle; 90% of those mITT patients randomized to HA and 91% randomized to vehicle completed the study. Eleven mITT patients randomized to HA discontinued the study early; of these, 7 completed the course of 5 injections. Of the 10 mITT patients randomized to vehicle who did not complete the study, 3 received all 5 injections. One patient in each group withdrew due to an adverse event. The study was carried out between February 1995 and August 1996.

**Demographics and baseline characteristics.** Fifty-six (56%) of patients in the HA group and 61% in the control group were female. The 2 treatment groups were similar with respect to age, weight, and height, with no statistical differences (Table 1).

In the modified ITT population, 69% of those in the HA group and 63% of those in the control group had OA in both knees. Sixty-six percent and 68% of patients in HA/control groups, respectively, reported having OA of other joints. Forty-seven percent of mITT patients randomized to receive HA reported having symptoms of knee OA for more than 5 years, 30% for 2–5 years, 18% for 1–2 years, and 5% for less than one year. In the control group, the proportions were similar, namely 50%, 30%, 10%, and 10%, respectively.

In the 3 months prior to entry to the study, 56% of mITT patients randomized to treatment with HA had taken analgesics for their symptoms of OA, 55% had taken NSAID, and 12% were under the care of a physiotherapist. Twenty-seven percent of the patients had taken other agents for their OA, commonly complementary agents and nutraceuticals. In the control group the figures were 68%, 45%, 16%, and 44%, respectively.

**Primary efficacy analysis — intention to treat population.** There was no significant "center by treatment" or "treatment by visit" interaction for any of the primary efficacy variables ( $p > 0.05$ ). It was therefore acceptable to include data from all visits and all centers in the repeated measures ANCOVA model. The covariate in the model was the baseline assessment of each variable. Baseline scores for each of the WOMAC variables (and for the Lequesne Index) were similar in the 2 treatment groups (Table 2 for WOMAC scores). The mean of each of the efficacy variables was adjusted using the ANCOVA model to account for variability in the baseline assessment.

Table 2 presents the mean difference between the treatments and the associated 95% confidence interval calculated from the repeated measurements ANCOVA of the primary outcome variables, WOMAC pain, WOMAC stiffness, and WOMAC disability (Weeks 6–13). Scores decreased considerably from baseline for both active and control treatments in the order of 50%. In addition, a significant difference ( $p < 0.05$ ) between the treatment groups was observed in WOMAC pain and WOMAC stiffness, and both variables improved substantially more than the prespecified effect size (10%). For WOMAC disability the difference between the scores did not achieve statistical significance ( $p = 0.064$ ), but the improvement relative to control was greater than the prespecified effect size. The same analysis for the secondary outcome variable, the Lequesne Index, revealed a difference of 0.91 (CI 1.77, 0.05;  $p < 0.05$ ).

There was a considerable effect of the control treatment, probably attributable at least in part to the removal of any effusion in the joint and the administration of the vehicle solution, a procedure that is standard in studies of this type.

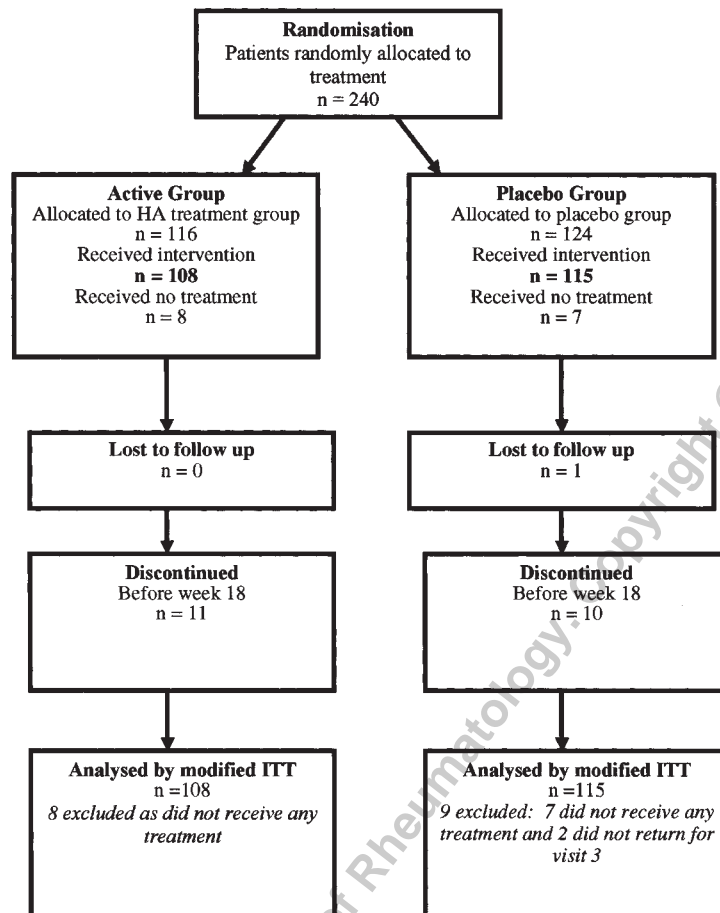


Figure 1. Modified CONSORT flowchart of patient disposition. Numbers of patients screened are not given.

Table 1. Demographic data for all subjects randomized.

	HA Group, n = 116	Controls, n = 124
Mean age, yrs (range)	62 (39–79)	62 (33–75)
Mean weight, kg (range)	84 (44–122)	80 (52–120)
Mean height, cm (range)	168 (149–188)	166 (143–191)
Female, %	56	61
Knee OA details*		
Left	17	23
Right	22	22
Both	77	79
Duration of symptoms**, yrs		
< 1	6	12
1–2	21	13
2–5	35	36
> 5	54	63

\* Not significantly different ( $p = 0.72$ ; chi-square). \*\* Not significantly different ( $p = 0.23$ ; chi-square).

Despite this, the adjusted mean scores were 15–18% lower than control in the HA group for all WOMAC scores, and 11% lower for the Lequesne Index score.

ANCOVA for WOMAC and Lequesne scores at each visit. In addition to the repeated measurements ANCOVA, an analysis of covariance was also performed on the data from Weeks 6, 10, 14, and 18, again using baseline values as the covariate and including a factor for study center. This analysis allowed an evaluation of the onset and duration of efficacy. There was no significant interaction between “treatment and center” at any visit. There was no significant difference between the treatment groups for any of the primary efficacy variables at Week 6, one week after completion of treatment. A significant difference in stiffness scores became apparent at Week 10, that is, 5 weeks after completion of treatment, and continued through Week 14, a further 4 weeks later. A significant difference between treatment groups was evident for WOMAC pain and for the Lequesne Index at Weeks 14 and 18, respectively; that is, 9 and 13 weeks after completion of treatment. For the WOMAC disability score a significant difference was evident only at Week 18. These data are presented in Table 3 and some of the variables are illustrated in Figures 2–5.

Other secondary measures of efficacy. Secondary measures

Table 2. Primary efficacy analysis using repeated measures ANCOVA (modified ITT analysis).

	Treatment	Baseline Scores		Scores During Treatment		Mean Difference	95% CI	p
		Mean	SD	Mean	SD			
<b>WOMAC Scale</b>								
<b>Pain</b>								
	HA	7.96	3.10	3.84	3.27	0.77	1.53, 0.02	0.045
	Controls	8.68	3.72	4.61	3.14			
<b>Disability</b>								
	HA	28.07	11.81	15.37	11.41	2.44	5.11, 0.22	0.064
	Controls	31.25	13.68	17.81	10.53			
<b>Stiffness</b>								
	HA	3.70	1.54	2.11	1.42	0.36	0.68, 0.03	0.024
	Controls	3.79	1.95	2.46	1.44			

Table 3. Mean difference between HA and control in WOMAC scores and Lequesne Index recorded at Weeks 6, 10, 14, and 18 adjusted for baseline variation using ANCOVA, and calculated using ANCOVA for repeated measures (Weeks 6–18). 95 % Confidence interval in parentheses.

	Week 6	Week 10	Week 14	Week 18
WOMAC	0.56	0.59	1.02*	0.93*
Pain	(1.40, -0.28)	(1.40, -0.22)	(1.85, 0.19)	(1.80, 0.06)
WOMAC	2.32	1.88	2.44	3.13*
Disability	(5.07, -0.42)	(4.74, -0.97)	(5.29, -0.41)	(6.09, 0.16)
WOMAC	0.25	0.44*	0.42*	0.32
Stiffness	(0.58, -0.08)	(0.83, 0.04)	(0.79, 0.05)	(0.71, -0.08)
Lequesne	0.53	0.79	1.23*	1.10*
Index	(1.37, -0.32)	(1.74, -0.17)	(2.19, 0.28)	(2.10, 0.10)

\* p < 0.05.

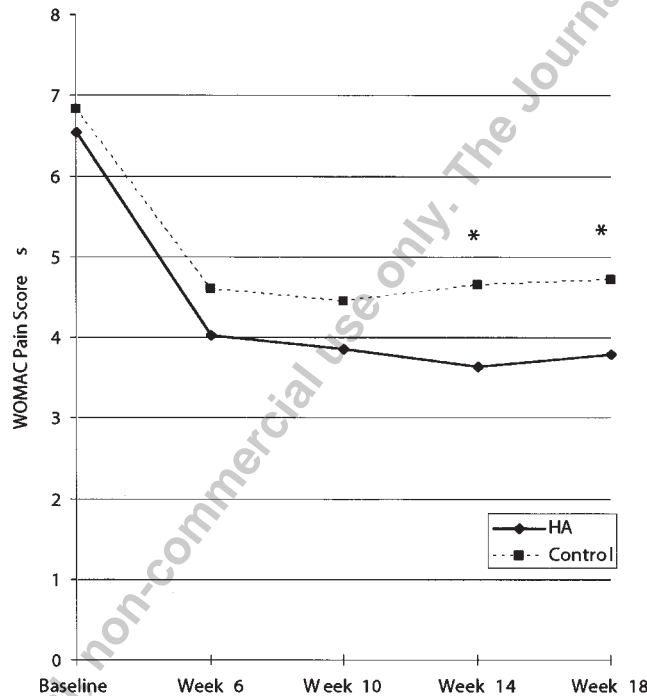


Figure 2. Treatment means for WOMAC pain scores at Weeks 6, 10, 14, and 18 adjusted for differences observed at baseline (ANCOVA); \*p < 0.05.

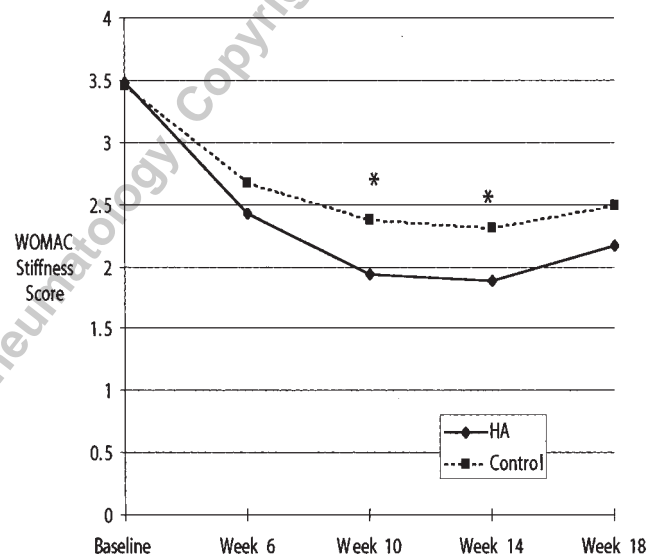


Figure 3. Treatment means for WOMAC stiffness scores at Weeks 6, 10, 14, and 18 adjusted for differences observed at baseline (ANCOVA); \*p < 0.05.

of efficacy, apart from Lequesne, were assessed using categorical scales and analyzed using a log-linear model analysis and the chi-square statistic adjusted for baseline values. These measures included examination of the treated joint at all visits (continuous or rest pain, pain when walking, crepitation on motion, degree of effusion), physician's assessment of global improvement (analysis of deviance from the log-linear model), and patient's assessment of global improvement (analysis of deviance from the log-linear model). There was no significant difference between treatments for any of these variables.

The secondary measures of efficacy assessed using a continuous variable (degree of flexion in the treated knee, degree of extension in the treated knee, and acetaminophen consumption associated with the treated knee) were analyzed using repeated measures ANCOVA including baseline measurements as the covariate. Statistically signif-

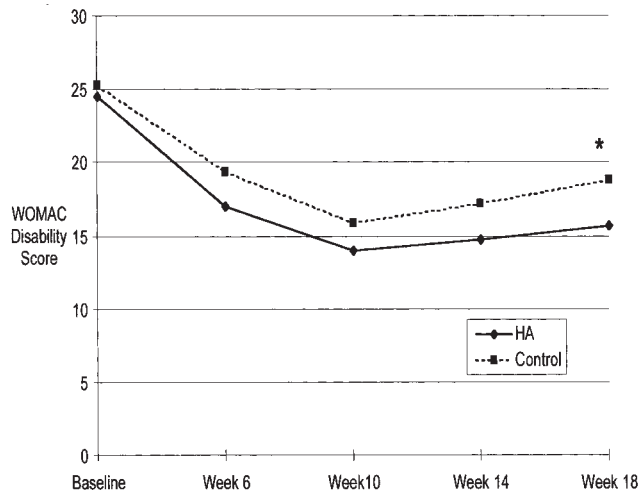


Figure 4. Treatment means for WOMAC disability scores at Weeks 6, 10, 14, and 18 adjusted for differences observed at baseline (ANCOVA); \* $p < 0.05$ .

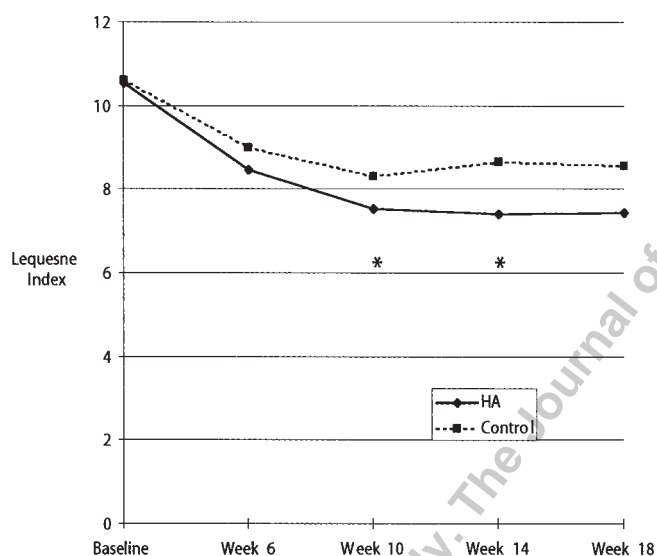


Figure 5. Treatment means for Lequesne Index at Weeks 6, 10, 14, and 18 with scores adjusted for differences observed at baseline (ANCOVA); \* $p < 0.05$ .

icant differences between the treatment groups were observed for the degree of flexion ( $p = 0.009$ ) and the degree of extension ( $p = 0.037$ ) in favor of the HA treated knee.

There was no difference between the treatment groups in the average daily acetaminophen consumption ( $p = 0.944$ ), and that was consistent across the treatment groups and throughout the study at 1.6 tablets per day. The consumption of analgesic and antiinflammatory medications for all indications during the study period was recorded. This consumption was discouraged and was not sanctioned by the protocol, in particular if the rationale for analgesic intake pertained to the knee being assessed as part of the

Table 4. Incidence of episodes of analgesic and antiinflammatory agent intake during the study.

Medication	HA Group	Controls	Total
Aspirin	4	9	13
Acetaminophen*	42	48	90
Codeine compounds	24	35	59
Dextropropoxyphene	1	11	12
NSAID	15	26	41
Methylprednisolone	2	5	7
Topical preparations	1	1	2
Herbal medicines	0	1	1
Physical therapy*	4	5	9

\* Other than that provided for in the protocol.

study. The overwhelming indication was pain elsewhere. Overall, therapy for pain and inflammation was instigated more frequently for control than HA, which would be expected to result in more favorable assessments in the control group and thus to reduce any differential effect of the HA (Table 4).

**Safety evaluation.** All patients who received one dose of the study drug (or control) and returned for evaluation at Week 2, i.e., one week after the first injection, are included in the safety analysis ( $n = 223$ ). A total of 482 adverse events were reported during the study. When only those events that were considered possibly, probably, or definitely related to study medication were examined, the type and incidence of these symptoms between the active and control groups was similar. The most frequent adverse event was injection site pain (HA group 16; controls 13). There were no serious adverse events considered to be possibly, probably, or definitely related to the study medication, and laboratory changes were unremarkable. Overall tolerance of the study regimen was excellent, as rated by the patients and physicians, and as indicated by the high proportion of patients completing the study. Ninety-six percent of HA patients and 94% of control patients completed the full treatment schedule.

## DISCUSSION

This controlled and blinded study of patients with mild to moderate OA of the knee followed for up to 13 weeks after last injection revealed that a regimen of 5 weekly IA injections of HA is both efficacious, in terms of pain and stiffness, and safe. These results were confirmed by a secondary outcome measure, the Lequesne Index. These findings were supported by an improvement in flexion and extension of the knee. The patients treated with HA demonstrated benefit up to 13 weeks after the last injection. This study was powered to detect differences based on previous estimates from OA trials using the WOMAC instrument<sup>32</sup>. Adjusted mean scores were 15–18% lower in the HA group for all

WOMAC variables and 11% lower for the Lequesne Index score. Recent reports have shown that these levels of changes in the WOMAC are greater than the minimal clinical improvement that is perceived by patients with knee and hip OA<sup>34,35</sup>.

The large response associated with aspiration and injection of saline vehicle, which is usual procedure in these studies, has been noted in previous HA studies<sup>25-27</sup>. The blinding of both patient and evaluator, as occurred in this study, is also important in evaluating control response.

This study attempted to define the OA cohort by including patients with predominant unilateral clinical disease. As well, an entry criterion for our study was that disease was mild to moderate and morbidly obese patients were excluded. Patients with predominant patellofemoral OA or clinically large effusions were excluded. These differences in inclusion criteria may account (together with the differences in primary outcome measure) for the discrepant result in a previous study using the same HA, which showed no difference between active and control treatments<sup>14</sup>. It is important that these study entry criteria be recalled before extrapolation to a general population of patients with OA of the knee.

The acceptability and safety of the treatment regimen was confirmed in this study. Over 90% of patients completed the 18 week study, the dropout rate being low in comparison to therapeutic trials in patients with OA over a comparable period, and 95% of patients received the full course of injections. Local pain and inflammation at the injection site occurred in roughly 10% of patients, but was usually considered mild and of short duration. This rate of injection site reaction compares favorably with reports of local HA toxicity using HA of different molecular weights<sup>11,36</sup>. There were no other adverse events or laboratory findings that were of concern and attributable to the study medication.

A possible weakness of this study is that some subjects used NSAID and analgesics that were not sanctioned by the protocol. The predominant motive, however, was pain in joints other than the index knee, but also pain elsewhere in the body. None were considered ineligible for analysis. The numerically greater episodes of use in the control group would have the apparent effect of reducing the positive effects of HA, thereby making it more difficult to show a clinically significant effect of HA.

Significant clinical uncertainties on the use of HA remain. Further studies on mechanism of action are required that might lead to more rational use. Of interest in this study and in some contrast to other studies with HA products, the onset of effect was slow, significant difference from control not being observed until after 6 weeks had elapsed. Cost-effectiveness issues need to be addressed, particularly as 5 injections were administered to patients in this study. Although the duration of followup after the last injection

was relatively short, it should perhaps be viewed in context of the short duration of effect of IA corticosteroids<sup>37</sup>. Determining which OA subgroups will have adequate responses and what might be the optimal number of injections in a course of treatment will need to be investigated. Importantly, although there is early data on the possible structure-modifying effects of HA<sup>13</sup>, there are also data from animal models of HA treatment that suggest loss of proteoglycan from cartilage, possibly related to increased weight-bearing in the damaged joint<sup>38,39</sup>. Again, further research is required.

In summary, our study has demonstrated efficacy and safety of intraarticular hyaluronan therapy in patients with mild to moderate, predominant unilateral OA knee, with pain relief persisting 13 weeks after a series of 5 injections.

#### ACKNOWLEDGMENT

We gratefully acknowledge the expert and dedicated contribution of the following rheumatologists and their associates: Peter Ryan and Indi Rasaratnam, The Alfred Hospital, Melbourne VIC; Russell Buchanan, Austin Hospital, Melbourne VIC; Rachele Buchbinder, Cabrini Hospital, Melbourne VIC; Kathryn Johns, Yael Kipen, and Geoffrey Littlejohn, Monash Medical Center, Melbourne VIC; Peter Nash and Clinton Herd, Nambour Hospital, Nambour QLD; James Bertouch, Prince of Wales Hospital, Sydney NSW; Kevin Pile, Queen Elizabeth Hospital, Adelaide SA; Michael Ahern, Repatriation General Hospital, Adelaide SA; Alexander Klestov, Royal Brisbane Hospital, Brisbane QLD; Ken Muirden, Royal Melbourne Hospital, Melbourne VIC; David Mathers and Gabor Major, Royal Newcastle Hospital, Newcastle NSW; Lyn March, Royal North Shore Hospital, Sydney NSW; Graeme Carroll and Patrick Hanrahan, Royal Perth Hospital, Perth WA; John Edmonds, St George Hospital, Sydney NSW; and Laurence Clemens, St Vincents Hospital, Melbourne VIC. We also thank Philip McCloud of Monash University Statistical Consulting Group, Monash University, Clayton, VIC, for expert statistical advice and service.

#### REFERENCES

1. Felts W, Yelin E. The economic impact of the rheumatic diseases in the United States. *J Rheumatol* 1989;16:867-84.
2. Altman RD, Hochberg MC, Moskowitz RW, et al. Recommendations for the medical management of osteoarthritis of the hip and knee. *Arthritis Rheum* 2000;43:1905-15.
3. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis. Report of a task force of the Standing Committee for International Clinical Studies including Therapeutic Trials (ESCISt). *Ann Rheum Dis* 2000;59:936-44.
4. Toole BP. Hyaluronan is not just a goo! *J Clin Invest* 2000;106:335-6.
5. Altman D. Laboratory findings in osteoarthritis. In: Moskowitz R, Howell D, Goldberg V, Mankin J, editors. *Osteoarthritis diagnosis and medical surgical management*. 2nd ed. Philadelphia: WB Saunders; 1992:313-28.
6. Pelletier JP, Martel-Pelletier J. The pathophysiology of osteoarthritis and the use of hyaluronan and hylan as therapeutic agents in viscosupplementation. *J Rheumatol* 1993;20 Suppl 39:19-24.
7. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol* 1993;20 Suppl 39:3-9.
8. Ghosh P, Smith M, Wells C. Second-line agents in osteoarthritis. In: Dixon JS, Furst DE, editors. *Second-line agents in the treatment of*

- the rheumatic diseases. New York: Marcel Dekker; 1992:363-427.
9. Adams ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of osteoarthritis. *J Rheumatol* 1993;20 Suppl 39:16-8.
  10. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology Oxford* 1999;38:602-7.
  11. Altman RD, Moskowitz R, and the Hyalgan study group. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomised clinical trial. *J Rheumatol* 1998;25:2203-12.
  12. Wobig M, Dickhut A, Maier R, Vetter G. Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. *Clin Ther* 1998;20:410-23.
  13. Listrat V, Ayrat X, Patarnello F, et al. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1997;5:153-60.
  14. Lohmander LS, Dalen N, Englund G, et al. Intra-articular hyaluronan injections in the treatment of osteoarthritis of the knee: a randomised, double blind, placebo controlled multicentre trial. *Ann Rheum Dis* 1996;55:424-31.
  15. Jones AC, Patrick M, Doherty S, Doherty M. Intra-articular hyaluronic acid compared to intra-articular triamcinolone hexacetonide in inflammatory knee osteoarthritis. *Osteoarthritis Cartilage* 1995;3:269-73.
  16. Adams ME, Atkinson MH, Lussier AJ, et al. The role of viscosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. *Osteoarthritis Cartilage* 1995;3:213-26.
  17. Dahlberg L, Lohmander LS, Ryd L. Intraarticular injections of hyaluronan in patients with cartilage abnormalities and knee pain. A one-year double-blind, placebo-controlled study. *Arthritis Rheum* 1994;37:521-8.
  18. Henderson EB, Smith EC, Pegley F, Blake DR. Intra-articular injections of 750 kD hyaluronan in the treatment of osteoarthritis: a randomised single centre double-blind placebo-controlled trial of 91 patients demonstrating lack of efficacy. *Ann Rheum Dis* 1994;53:529-34.
  19. Dougados M, Nguyen M, Listrat 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.
  20. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicenter, double-blind study. *Osteoarthritis Cartilage* 1993;1:233-41.
  21. Dixon AS, Jacoby RK, Berry H, Hamilton EBD. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Curr Med Res Opin* 1988;11:205-13.
  22. Uebelhart D, Williams JM. Effects of hyaluronic acid on cartilage degradation. *Curr Opin Rheumatol* 1999;11:427-35.
  23. George E. Intra-articular hyaluronan treatment for osteoarthritis. *Ann Rheum Dis* 1998;57:637-40.
  24. 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.
  25. Towheed TE, Hochberg MC. A systematic review of randomised controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. *Semin Arthritis Rheum* 1997;26:755-70.
  26. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. *Baillieres Clin Rheumatol* 1997;11:769-94.
  27. Brandt KD, Smith GN, Simon LS. Intraarticular injection of hyaluronan as treatment for knee osteoarthritis. *Arthritis Rheum* 2000;43:1192-203.
  28. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis. Hope, hype and hard truths. *Arch Intern Med* 2002;162:245-7.
  29. Pasquali-Ronchetti I, Guerra D, Taparelli F, et al. Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. *Rheumatology Oxford* 2001;40:158-69.
  30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. 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.
  31. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation – value in comparison with other assessment tests. *Scand J Rheumatol* 1987;65 Suppl:85-9.
  32. Bellamy N, Kean WF, Buchanan WW, Gerecz-Simon E, Campbell J. Double blind randomised controlled trial of sodium meclofenamate (Meclomen) and diclofenac sodium (Voltaren): post validation reapplication of the WOMAC Osteoarthritis Index. *J Rheumatol* 1992;19:153-9.
  33. Bellamy N. Musculoskeletal clinical metrology. Lancaster: Kluwer Academic Publishers; 1993:1-367.
  34. Ehrlich EW, Davies GM, Watson DJ, et al. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire and global assessments in patients with osteoarthritis. *J Rheumatol* 2000;27:2635-41.
  35. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life instruments in patients with osteoarthritis of the lower extremities. *Arthritis Rheum* 2001;44:384-91.
  36. 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.
  37. Ravaut P, Moulinier L, Giraudeau B, et al. Effects of joint lavage and steroid injections in patients with osteoarthritis of the knee: results of a multicentre, randomized, controlled trial. *Arthritis Rheum* 1999;42:475-82.
  38. Ghosh P, Read R, Numata Y, Smith S, Armstrong S, Wilson D. The effects of intraarticular administration of hyaluronan in a model of early osteoarthritis in sheep. II. Cartilage composition and proteoglycan metabolism. *Semin Arthritis Rheum* 1993;22:31-42.
  39. Smith GN, Myers SL, Brandt KD, Mickler EA. Effect of intraarticular hyaluronan injection in experimental canine osteoarthritis. *Arthritis Rheum* 1998;41:976-85.