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OSTEOARTHRITIS and CARTILAGE

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

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Summary

To determine the safety and efficacy of viscosupplementation with hylan G-F 20, a cross-linked hyaluronan preparation, used either alone or in combination with continuous non-steroidal anti-inflammatory drug (NSAID) therapy, a randomized, controlled, multicenter clinical trial, assessed by a blinded assessor, was conducted in 102 patients with osteoarthritis (OA) of the knee. All patients were on continuous NSAID therapy for at least 30 days prior to entering the study. Patients were randomized into three parallel groups: (1) NSAID continuation plus three control arthrocenteses at weekly intervals; (2) NSAID discontinuation but with three weekly intra-articular injections of hylan G-F 20; and (3) NSAID continuation plus three injections, one every week, intra-articular injections of hylan G-F 20. Outcome measures of pain and joint function were evaluated by both the patients and an evaluator at baseline and weeks 1, 2, 3, 7 and 12, with a follow-up telephone evaluation at 26 weeks. At 12 weeks all groups showed statistically significant improvements from baseline, but did not differ from each other. A statistical test for equivalence, the q-statistic, demonstrated that viscosupplementation with hylan G-F 20 was at least as good or better than continuous NSAID therapy for all outcome measurements except activity restriction. At 26 weeks both groups receiving hylan G-F 20 were significantly better than the group receiving NSAIDs alone. A transient local reaction was observed in three patients after hylan G-F 20 injection; only one patient withdrew from the study as a result and all recovered without any sequela.

Hylan G-F 20 is a safe and effective treatment for OA of the knee and can be used either as a replacement for or an adjunct to NSAID therapy.

Key words: Osteoarthritis, Viscosupplementation, Hylan, Therapy.

Introduction

Osteoarthritis (OA) is common and costly [1, 2]. OA affecting the knee is especially troublesome. While OA is characterized pathologically by deterioration and loss of the articular cartilage, subchondral sclerosis and osteophyte formation, and is often accompanied by inflammation of the synovium, deterioration of the supporting structures of the joint and a multitude of other pathological features [3–5], it is mainly pain and loss of function that lead patients with OA to seek medical attention [6]. At present, no medical or physical therapy has been shown convincingly to affect the rate of the deterioration of the affected joint structures in humans, so therapeutic efforts are rightly directed to symptomatic relief of pain and attempts to preserve joint function. Many types of treatment have a role in the management of the pain of OA. These include symptomatic pharmacological treatment with analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections, muscle strengthening exercises, weight loss, the use of devices, such as canes and orthotics, arthroscopic joint debridement, joint lavage, total joint replacement, education and counseling [7, 8].

While analgesics may be as effective as NSAIDs in treating some patients with OA of the knee [9, 10],

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NSAIDs are considered a standard treatment for OA. Unfortunately, many patients either cannot tolerate NSAIDs or suffer serious NSAID-induced side-effects, predominantly gastrointestinal ulceration and bleeding [11–14]. The frequency of NSAID-associated side effects has led to the use of cytoprotective agents to improve their safety profile [15–17]. Within this context, a re-evaluation of the role of NSAIDs in the overall management of OA seems appropriate.

It has been known for many years that synovial fluid from osteoarthritic joints is lower in elasticity and viscosity than that from normal joints [18, 19]. This decrease in the rheological properties of the synovial fluid results from reductions in the molecular size and concentration of hyaluronan in the synovial fluid [19]. This phenomenon led Balazs to introduce viscosupplementation therapy [20], which is the injection of hyaluronan or its derivatives in an attempt to return the elasticity and viscosity of the synovial fluid to normal or higher levels [21]. While viscosupplementation with hyaluronan is not 'mainstream' therapy for OA of the knee in North American clinical practice, it has been used extensively elsewhere, especially in Italy and Japan, and has been the subject of numerous clinical trials (reviewed in [22]). From that experience, viscosupplementation with hyaluronan has been shown to be a safe treatment of OA of the knee, although six to 10 injections are often required to achieve efficacy [22]. Possible reasons why so many injections are required are that the elastoviscous properties of current hyaluronan preparations are inadequate to restore sufficiently the elasticity and viscosity of the synovial fluid in the arthritic knee, or that the injected hyaluronan is eliminated too quickly from the joint to be effective. Both of these mechanisms depend upon the rheological properties of the hyaluronan, which in turn depend upon its molecular weight. The results of viscosupplementation therapy might therefore be expected to depend upon the rheological properties and molecular weight of the hyaluronan preparation [23].

Because of this limitation in viscosupplementation with hyaluronan preparations, hylans (chemically cross-linked hyaluronans) were developed to improve the efficacy of viscosupplementation therapy of OA [24]. Cross-linking hyaluronan improves its utility for viscosupplementation in several ways. First, the rheological properties are increased [25]; second, it has a longer retention time in the synovial space [24]; and third, because of the cross-links, it becomes more resistant to free radical degradation [26]. One particular combination of hylans, hylan G-F 20 (Synvisc®), has been developed specifically as a device for viscosupplementation therapy in OA of the knee.

Initial studies have shown that injections of hylan G-F 20 are safe and effective [27]. In a double-blind controlled study involving 50 patients, two injections of hylan G-F 20 administered 2 weeks apart were shown to be effective in relieving the pain of OA of the knee [27]. In a similar study involving 30 patients, a treatment regimen consisting of three injections of hylan G-F 20 given 1 week apart was significantly better than saline injections, and gave more pain relief than the two-injection regimen from the previous study [27]. The efficacy of a therapeutic regimen of three weekly injections of hylan G-F 20 was further demonstrated in a randomized, double-blind, controlled clinical trial with 118 patients. In many of the patients the beneficial results were maintained for as long as 26 weeks [28]. Thus, hylan G-F 20 has been shown to be significantly more effective than saline injections in three randomized double-blind trials. Additional safety data was accumulated in an open-label trial involving 221 patients. In all four of these trials, for a total 1028 injections, there were only 17 possibly-related adverse reactions, all of which were local and transient. Thus, hylan G-F 20 appears to be an effective and safe treatment for OA of the knee. (For a review see [28].)

Clearly, if it is appropriate to re-evaluate the role of NSAIDs in the therapy of OA, then the role of hylan G-F 20 must be evaluated with respect to its role in concomitant or separate treatment of OA with NSAIDs. To accomplish this, a three-arm multicenter, randomized, blinded clinical trial was performed. The purpose of the study was to evaluate the safety and effectiveness of three weekly intra-articular injections of hylan G-F 20 in an affected knee in patients with OA of the knee and to compare this treatment with that of continuous oral NSAID therapy in both the presence and absence of hylan G-F 20 viscosupplementation.

Materials and methods

PATIENTS

Inclusion criteria

The patients had to be men or women aged 18–75 years with a diagnosis of chronic idiopathic OA of the knee on radiographic examination. A Kellgren-Lawrence radiographical grade of 1 or 2 or 3 in no more than two compartments (and not a grade 3 in the patellofemoral compartment) was required [29]. In addition, patients had to satisfy at least four of the following six criteria: (1) erythrocyte sedimentation rate <30 mm/h; (2) rheumatoid factor titer $<1:160$; (3) morning

stiffness not longer than 30 min; (4) crepitus on active motion; (5) tenderness of the bony margins; and (6) physician determination of absence of rheumatoid disease. Furthermore, they needed to have been tolerant of NSAID treatment for at least the 30-day period preceding the trial without significant side effects, to have been using the joint actively on a daily basis and to have a score of >50 mm on a 100 mm visual analog scale (VAS) for pain on motion with weight-bearing, which was the primary efficacy variable. The study protocol also allowed for any patient who suffered sufficient pain in both knees to be treated in both knees, with only the most painful knee to be considered to be enrolled in the study and evaluated as to efficacy criteria, while both knees were evaluated for safety.

Exclusion criteria

Patients were excluded if they had any other serious systemic disease, depression, or neuroses, acute synovitis or excessive effusion, were clinically obese (>30% above normal body weight), had a varus or valgus deformity of >15° (as measured on the radiograph), were pregnant or not using an effective form of contraception (if of child-bearing potential), were on chronic daily steroid therapy, or had surgery or a joint injection within the previous 3 months.

TRIAL DESIGN

The study was 12 weeks in duration, with a follow-up telephone interview at 26 weeks. The schedule of treatments and visits is shown as a time line in Fig. 1. Patients eligible for the study were randomly assigned to one of three treatment groups. One treatment group (NSAID-only) received a series of three weekly arthrocenteses and was instructed to continue taking their usual NSAID for the duration of the study. A second treatment group (hylan G-F 20-only) discontinued their usual NSAID, but instead received three weekly intra-articular injections of 2.0 ml of hylan G-F 20. The third treatment group (hylan G-F 20 + NSAID) continued their usual NSAID therapy and received three weekly 2.0 ml intra-articular injections of hylan G-F 20. No placebo group was included because of ethical constraints and because the goal of the study was to compare the efficacy of hylan G-F 20 with an established therapeutic modality. Furthermore, the efficacy of hylan vs placebo had been established in the prior clinical trials [28]. All patients were instructed that if the pain became unbearable they could take acetaminophen as 'rescue' analgesia and were to report the usage of their medication to the evaluator at the next follow-up visit. All patients were also instructed that for the duration of the study they were not to receive any additional medication, i.e. no steroids, NSAID other than their usual one (if in the first or third treatment group) and, no analgesic other than acetaminophen. The extent of acetaminophen usage was documented using weekly diaries completed by the patients and collected by the investigators.

Patients in the hylan G-F 20-only group may have been able to surmise their group assignment from their instruction to discontinue NSAID therapy. If this incomplete blinding introduced a bias, it would be against the hylan G-F 20-only group in that patients recognized that they were discontinuing an active medication, and consequently may have expected their condition to worsen.

Patients were initially seen and evaluated for suitability 1 week before treatment initiation. Patients were evaluated prior to the injections of the week 1 (baseline), 2 and 3 visits and at post-treatment weeks 7 and 12. After 12 weeks the patients were not specifically instructed with respect to NSAID therapy. To obtain data regarding the duration of action of hylan G-F 20, the patients were contacted by a telephone interview at post-treatment week 26, and were requested by the evaluator to rate, as if it were on a VAS the same variables that had been evaluated by the patients in the previous study visits and to evaluate the ordinal variables. They were also queried concerning NSAID use and any other treatments of OA. Finally, they were asked if their pain had returned to pre-study level between weeks 12 and 26.

Patients receiving hylan G-F 20 treatment were injected intra-articularly with 2.0 ml of hylan G-F 20 at each visit for three consecutive weeks (weeks 1, 2 and 3). Any effusion present in the joint was withdrawn prior to treatment. For the patients

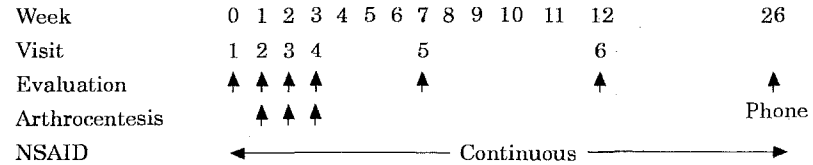

FIG. 1. Flow chart of the study procedures. NSAID, non-steroidal anti-inflammatory drug.

in the NSAID-only group, the needle of the syringe was inserted intra-articularly, any effusion present in the joint was withdrawn, but nothing was injected. To insure that blinding was maintained, a screen was provided so that the patient could not observe the treatment. Furthermore, the evaluator, who was unaware of each patient's treatment group, was not to be present at the time or place of each weekly injection.

OUTCOME MEASURES

Efficacy

Each of the following efficacy variables was measured at all evaluation visits using a 100 mm VAS [30]: pain on motion with weight-bearing; pain at rest; pain at night; restriction of activity; patient's overall assessment of arthritic pain; pain during a 50 foot walk; medial joint tenderness; lateral joint tenderness; and evaluator's overall assessment of the treatment. Pain on motion with weight-bearing was the primary efficacy variable. Efficacy variables that were measured on an ordinal scale (1 = never able to perform; 2 = occasionally able to perform, and 3 = frequently able to perform) were the level of activity for each of standing, sitting, walking and climbing stairs. The severity of the patient's pain was also rated categorically by the patient at baseline and at post-treatment weeks 1, 2, 3, 7 and 12 as; 1 = none; 2 = pain only on starting the activity after rest; 3 = pain during the day when active; 4 = pain during the day, at rest; or 5 = pain all day and waking the patient at night. For all analyses which were compared to baseline, the measurements taken immediately before treatment at week 1 were considered to be the baseline.

Safety

Data regarding safety and adverse events were obtained by interviewing the patients at each study visit as to any adverse event experienced since the previous visit. The investigator was also instructed as to the criteria for identifying whether an adverse event was to be considered as treatment related. All adverse events were to be reported on the appropriate patient assessment of pain as an indication of success. Study sites and participating personnel were instructed uniformly as to the manner in which the study should be conducted according to Good Clinical Practice (GCP) guidelines [31, 32], including the completion of the patient informed consent form, a review of the study protocol and the manner in which patient case report forms were to be completed.

STATISTICAL ANALYSIS

Sample size was determined using a criterion of a 25% improvement in the patient's or evaluator's global assessment of pain as an indication of success. Based on this, 80% of the two active treatment groups (hylan G-F 20, alone or with NSAID), as compared to a projected 50% of the 'control' group (NSAID alone), were expected to show success. Sample size was then to be based on a comparison of the three treatment groups, using a significance level of $P = 0.05$ and a power of 0.80. Thus, the planned sample size was 26 patients per treatment group, or a total of 78 patients.

Efficacy was analyzed both for the 'evaluable' patient population, i.e. limited to those patients fulfilling all inclusion and exclusion criteria and receiving a full course of three hylan G-F 20 injections and for the 'intent-to-treat' patient population, i.e. including any patient receiving at least one arthrocentesis (NSAID-only group) or one hylan G-F 20 injection. With respect to efficacy analyses, this report focused on the 'evaluable' patient population, making reference to the 'intent-to-treat' patient population only where relevant differences occur. With respect to safety analysis, this report focused on the 'intent-to-treat' patient population, so as to capture data for any patient exposed to the test device.

Data to be analyzed were entered from the case report forms into a database and subjected to quality assurance procedures that were double verified and corrected. Improvements from baseline were calculated for individual patients. The baseline used for all calculations of improvement was the score obtained at week 1 just prior to the first intra-articular treatment.

Categorical analyses were performed for each outcome measure, defining improvement to a VAS score below 20 mm as a symptom-free score, in order to analyze the difference between the treatment groups with respect to the percentage of symptom-free patients at 26 weeks.

Analysis of variance (ANOVA) was used for analysis of continuous data and comparisons among the three treatment groups. Fisher's LSD multiple comparisons test was used to distinguish between individual treatments. Paired t-tests were used to evaluate efficacy by comparing pre-treatment values with post-treatment observations. The chi-squared test and tests of proportions were used to analyze the categorical data. For the severity of pain variable, which did not follow a continuous distribution, ANOVA of ranked data was used. Least squares means were calculated from the individual

patient improvements and used for comparisons among the three treatment groups. All analyses were performed using SAS software (SAS Institute, Cary, NC, U.S.A.). ANOVA was obtained using PROC GLM, with the exception of the binomial approximation to the normal distribution (Z statistic) using categorical analysis tables [33].

The so-called q-statistical analysis [34] was used to evaluate whether or not this study could detect a difference among the treatments (i.e. to evaluate the probability of a type II error). The q-statistical analysis is a one-tailed test against the null hypothesis that the test treatment is inferior to the active control treatment. The q-statistic is the ratio of the mean improvement of the test treatment to the control treatment, and the ql-statistic is the ratio of the lower 95% confidence limit of the improvement from baseline of the test treatment to the improvement from baseline of control treatment. In general, studies of adequate size that are assessing treatments with similar effects, the ql-values are 0.60 or above. In other words, there is a 95% confidence that the test treatment is at least 60% as effective as the control [34]. For this study the test group was the hylan G-F 20 only group and the control group was the NSAID-only group. The mean square error and least-squares means were calculated from the ANOVA model to produce ql, the lower 95% confidence limit of this ratio.

Results

PATIENTS

Demographic features

One hundred and two patients entered the trial and received at least one arthrocentesis or injection of hylan G-F 20 (the 'intent-to-treat' patient population). Ninety-three patients completed all three intra-articular treatments and complied with all elements of the protocol (the 'evaluable' patient population); 32 in the NSAID group, 28 in the hylan G-F 20 group and 33 in the hylan G-F 20 + NSAID group. Eighty-nine of the 93 evaluable patients completed the week 12 follow-up assessment and 90 completed the week 26 telephone interview. In general, the conclusions drawn from data for both populations were the same.

The demographic characteristics of the 'intent-to-treat' patient population (the entire study population) are presented in Table I(a); there are no significant differences between the treatment groups. The duration of disease and X-ray grade for the 'intent-to-treat' patient population are presented in Table I(b). With respect to duration of disease, a statistically significant difference was found favoring the two hylan G-F 20 groups. Disease duration did not correlate with clinical symptoms [35], and the three groups are very similar with respect to their baseline scores on efficacy outcome measures (see below). Sixteen of the patients had only grade 1 radiological changes, but they all had VAS scores >50 mm for pain on motion at baseline (mean 64.1 ± 2.4) for pain on motion. Thus, these patients almost certainly had OA [36]. Thirteen patients were treated bilaterally, but efficacy was assessed only on the more severely affected knee, while safety was assessed on both injected knees.

Efficacy

BASELINE DATA

Baseline scores for all outcome measures used in the analysis of efficacy are show in Table II. Statistically significant differences between the treatment groups were only found for pain at night and support used. The baseline scores illustrate the clinical symptoms of the study population. Patient evaluations of pain on motion, restriction of activity and overall pain were consistently above an average VAS score of 50 [Table II(a)]. The measurement of severity of pain showed mean values between 3 and 4 at baseline, indicating an intensity between pain during the day when active and pain during the day at rest. The measurement of level of activity/running showed mean values between 2 and 3 for all three groups, indicating an activity level between occasionally able to run and never able to run. All other level of activity measurements (standing, sitting, walking and climbing) were always below a mean ordinal score of 2, indicating that most patients were occasionally, and some frequently, capable of these activities. Evaluator assessments [Table II(b)] revealed a similar degree of symptoms, with only pain on walking, which was an inclusion criterion, and overall clinical assessment having mean baseline scores >50 mm on the VAS.

Most patients were not inhibited from the performance of everyday activities, thus the scores for the levels of activity were already so low that no change could be measured, and this limited their usefulness, i.e. they were insensitive to change. Furthermore, the baseline VAS scores were generally relatively higher than the measures using an ordinal scoring system, and so a change in their level with the treatments could be measured. The useful outcome measures of the study were the scores for pain with motion, pain at rest, pain at night, restriction of activity and overall evaluation of arthritic pain rated by the patient using the VAS

Table I(a)
Demographic data summary for the intent-to-treat patient population

Parameter	Population: NSAID $N=34$	Hylan G-F 20 $N=31$	Hylan G-F 20 +NSAID $N=37$	Total $N=102$
Sex				
Male	11 (32%)	10 (32%)	15 (41%)	36 (35%)
Female	23 (68%)	21 (68%)	22 (59%)	66 (65%)
Age at treatment (years)				
Mean ± S.E.M.	63 ± 2	61 ± 2	60 ± 2	61 ± 1
Median	64	62	63	63
Range	37–76	35–74	38–75	35–76
Height (in)				
Mean ± S.E.M.	68 ± 0.6	65 ± 0.6	67 ± 0.8	66 ± 0.4
Median	65	64	66	65
Range	60–73	59–75	57–77	57–77
Weight (lb)				
Mean ± S.E.M.	156 ± 4	162 ± 5	164 ± 6	160 ± 3
Median	158	166	161	160
Range	118–196	120–250	107–262	107–262

There were no significant differences among the groups. NSAID, non-steroidal anti-inflammatory drug.

Table I(b)
Disease characteristics at baseline as mean in years ± S.E. and radiographical grade as number of patients in each grade and the percentage of the total group at baseline for the 'intent-to-treat' patient population

Parameter	Population: NSAID $N=34$	Hylan G-F 20 $N=31$	Hylan G-F 20+ NSAID $N=37$	Total $N=102$
Duration of joint desease				
Mean ± S.E.	8 ± 1*	5 ± 0.8	5 ± 0.6	6 ± 0.6
X-ray grade (compartment)				
Medial				
1	11 (32%)	8 (27%)	8 (22%)	27 (27%)
2	17 (50%)	14 (47%)	17 (47%)	48 (48%)
3	6 (18%)	8 (27%)	11 (31%)	25 (25%)
Lateral				
1	20 (61%)	13 (46%)	22 (71%)	55 (60%)
2	10 (30%)	12 (43%)	8 (26%)	30 (32%)
3	3 (9%)	3 (11%)	1 (3%)	7 (8%)
Patellofemoral				
1	18 (56%)	14 (45%)	25 (71%)	57 (58%)
2	14 (44%)	17 (55%)	10 (29%)	41 (42%)
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Indicates the only statistically significant difference among these groups: disease duration was longer for the NSAID-only group than for either of the hylan G-F 20- treated groups ($P=0.025$). NSAID, non-steroidal anti-inflammatory drug.

and the scores for medial joint tenderness, lateral joint tenderness, pain while walking and overall assessment of clinical condition rated by the evaluator on the VAS.

EFFICACY VS. BASELINE

Table III(a) presents the mean improvement scores at week 12 for each of the key outcome

Table II(a)
Scores of the outcome measures at baseline—outcome measures evaluated by the patients. The numbers are the raw visual analog scale numbers ± S.E. The P values are for the intergroup comparisons

Outcome measure	NSAID ($N=33$)	Hylan G-F 20 ($N=29$)	Hylan G-F 20+ NSAID ($N=34$)	*P*-value: Hylan G-F 20 vs NSAID	*P*-value: Hylan G-F 20+ NSAID vs NSAID	*P*-value: Hylan G-F 20 +NSAID vs hylan G-F 20
Pain with motion	63 ± 3	61 ± 3	60 ± 3	NS	NS	NS
Pain with rest	29 ± 4	36 ± 4	26 ± 4	NS	NS	NS
Pain at night	34 ± 5	35 ± 5	20 ± 5	NS	0.048	0.041
Severity of pain	3.3 ± 0.2	3.3 ± 0.2	3.1 ± 0.2	NS	NS	NS
Restriction of activity	60 ± 4	53 ± 5	51 ± 4	NS	NS	NS
Overall assessment of arthritic pain	62 ± 3	62 ± 3	57 ± 3	NS	NS	NS
Support used	1.4 ± 0.08	1.1 ± 0.09	1.1 ± 0.08	0.022	NS	NS
Standing/walking						
Level of activity (standing)	1.2 ± 0.06	1.1 ± 0.07	1.1 ± 0.06	NS	NS	NS
Level of activity (sitting)	1.2 ± 0.08	1.4 ± 0.09	1.4 ± 0.08	NS	NS	NS
Level of activity (walking)	1.2 ± 0.08	1.4 ± 0.08	1.2 ± 0.08	NS	NS	NS
Level of activity (climbing)	1.7 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	NS	NS	NS
Level of activity (running)	2.7 ± 0.08	2.8 ± 0.09	2.6 ± 0.08	NS	NS	NS

NSAID, non-steroidal anti-inflammatory drug; NS, not significant.

Table II(b)
Scores of the outcome measures at baseline—outcome measures evaluated by the assessor. The numbers are the mean visual analog scale scores ± S.E. The P values are for the intergroup comparisons

Outcome measure	NSAID ($N=33$)	Hylan G-F 20 ($N=29$)	Hylan G-F 20+ NSAID ($N=34$)	*P*-value: Hylan G-F 20 vs NSAID	*P*-value: Hylan G-F 20+ NSAID vs NSAID	*P*-value: Hylan G-F 20+ NSAID vs hylan G-F 20
Effusion	19 ± 3	16 ± 3	14 ± 3	NS	NS	NS
Medial joint tenderness	45 ± 4	44 ± 4	37 ± 4	NS	NS	NS
Lateral joint tenderness	36 ± 4	38 ± 4	33 ± 4	NS	NS	NS
Pain while walking	57 ± 4	53 ± 4	49 ± 4	NS	NS	NS
Overall assessment	59 ± 3	55 ± 3	54 ± 3	NS	NS	NS
50 foot walk time	13 ± 1	13 ± 1	13 ± 1	NS	NS	NS

NSAID, non-steroidal anti-inflammatory drug; NS, not significant.

measures of the study. Over the 12-week course of study, the patients in all three treatment groups experienced improvements that were both highly statistically significantly different ($P < 0.01$) and clinically important by standardized criteria [37]. When comparing the improvement scores among the three treatment groups, patients in the two hylan G-F 20 groups generally improved more than the patients in the NSAID-only group. This was true for all outcome measures except activity restriction, medial tenderness and pain at night. However, this nominally greater efficacy for the hylan G-F 20 groups was usually not statistically significantly different. The only outcome measure to show a statistically significant difference between the groups was pain at rest, for which the hylan G-F 20-only group improved significantly more than the NSAID-only group ($P = 0.05$).

Fourteen patients in the 'evaluable' patient population (15%) presented with a synovial effusion greater than 2.0 ml at the first intra-articular treatment. Five were randomized to the NSAID-only group, seven to the hylan G-F 20-only group and two to the hylan G-F 20 + NSAID group. By the last treatment visit (week 4) a clinically detectable effusion was absent in all but one of the patients,

Table III(a)

Mean improvements at week 12 for the outcome measures evaluated by the patients and those evaluated by the blinded assessor. All mean improvements were highly statistically significantly different from the baseline values (P < 0.01)

	Mean improvement		
	NSAID ($N=32$)	Hylan G-F 20 ($N=25$)	Hylan G-F 20 + NSAID ($N=32$)
Outcome measure evaluated by the patient			
Pain with motion	19 ± 4	23 ± 4	26 ± 4
Pain at rest	9 ± 4	19 ± 4	12 ± 4
Pain at night	13 ± 4	21 ± 5	10 ± 4
Restriction of activity	14 ± 5	13 ± 6	14 ± 5
Overall assessment of arthritic pain	19 ± 5	24 ± 5	26 ± 4
Outcome measure evaluated by the assessor			
Medial joint tenderness	14 ± 4	19 ± 4	10 ± 4
Lateral joint tenderness	9 ± 4	17 ± 5	12 ± 4
Pain while walking	19 ± 4	27 ± 5	22 ± 4
Overall assessment of clinical condition	16 ± 3	24 ± 4	22 ± 3

NSAID, non-steroidal anti-inflammatory drug.

Table III(b)

q-Statistical analysis of improvement at week 12, both those evaluated by the patient and those evaluated by the blinded assessor. The hylan G-F 20-only group (test group) is compared vs the non-steroidal anti-inflammatory drug (NSAID)-only group (control group). The q value is the ratio of the improvement from baseline of the group to the improvement from baseline of the control groups. The ql value is the ratio of the lower 95% confidence limit of the improvement from baseline of the test group to the improvement from baseline of the control group. This value represents minimum equivalent efficiency of hylan G-F 20 therapy compared with NSAID therapy. See text for details

	q-Statistical values	
	q (hylan G-F 20-only vs NSAID-only)	ql (hylan G-F 20-only vs NSAID-only)
Outcome measure evaluated by patients		
Pain with motion	1.24	0.71
Pain at rest	2.26	1.19
Pain at night	1.58	0.74
Restriction of activity	0.89	<0.01
Overall assessment of arthritic pain	1.23	0.63
Outcome measure evaluated by assessor		
Medial joint Tenderness	1.36	0.68
Lateral joint Tenderness	1.78	0.72
Pain while walking	1.44	0.89
Overall assessment of clinical condition	1.44	0.90

NSAID, non-steroidal anti-inflammatory drug.

who was in the hylan G-F 20 + NSAID group. Thus, in this patient population, synovial effusions resolved by the third arthrocentesis, whether or not the patients were treated with continuous NSAID therapy or with viscosupplementation with hylan G-F 20. Furthermore, a separate statistical analysis of efficacy for the patients with effusions demonstrated that they did as well clinically as patients that presented without an effusion (data not shown).

ASSESSMENT OF EQUIVALENCY

Because all the treatments were effective at 12 weeks, essentially without any statistically significant differences, it was necessary to analyze the

ability of the study to have detected a difference among the treatments. One approach to this is to determine the lower 95% confidence limit of the ratio of the least mean squared improvements from baseline for the efficacy variables of the test treatment to the control treatment. This type of analysis, the so called q-statistical analysis, is one way suggested by U.S. regulatory agencies to evaluate the therapeutic equivalence of similar pharmaceutical agents [34]. A ql value (the lower confidence limit of the improvement ratio) of 0.6 is the minimal value that can be considered to demonstrate therapeutic equivalence [34]. Therefore, q-statistical analysis was performed to determine whether or not, with 95% confidence, the efficacy of hylan-only treatment was greater than or equal to the efficacy of NSAID-only treatment. The q values reported in Table III(b) are defined as the ratio of the least mean square improvement for the hylan-only group to that for the NSAID-only group. The q values are >1 for every outcome measure except activity restriction, because the magnitude of improvement is greater in the hylan G-F 20-only group. The last column of Table III lists the ql values. These are >0.60 for all values except restriction of activity. Thus, the hylan G-F 20-only and NSAID-only groups can be considered equivalent, to a 95% confidence level, for all outcome measures except activity restriction.

FOLLOW-UP BETWEEN WEEKS 12 AND 26

Patients were instructed to telephone the investigator if their pain returned to its pre-study level. None of the patients in the hylan G-F 20 + NSAID group reported a return of pain to pre-study levels, compared with five (16%) of the NSAID-only patients and seven (26%) of the hylan G-F 20-only patients. The superiority of the hylan G-F 20 + NSAID group in this respect was statistically significant ($P = 0.019$).

Resumption or discontinuation of NSAID therapy was also monitored between weeks 12 and 26. Only one patient (3%) in the NSAID-only group discontinued NSAID therapy, compared to five (16%) of the hylan G-F 20 + NSAID group, but this difference was not statistically significant. In the hylan G-F 20-only group, 12 (44%) of the patients were able to completely refrain from NSAID therapy for the entire 26 weeks. This difference between the hylan G-F 20-only group and the two NSAID groups was statistically significant, but these differences are at least partially attributable to the study design.

26 WEEK FOLLOW-UP

The longer term efficacy of viscosupplementation with hylan G-F 20 was assessed by a telephone interview between the evaluator and the patient 24 weeks after the last arthrocentesis or hylan G-F 20 injection. Because the method of assessment at 26 weeks differed from that at baseline, improvement scores at week 26 could not be calculated relative to the baseline scores. The mean VAS scores at week 26 for the three treatment groups are presented in Table IV. Only the patient-evaluated VAS variables were determined, because the evaluator was judging the patient's perception of clinical condition, rather than performing a personal evaluation. As was observed at the week 12 endpoint, both hylan G-F 20 groups consistently showed better scores than the NSAID-only group. But in contrast to the week 12 endpoints, there were a number of statistically significant differences in the hylan G-F 20-only group vs the NSAID-only group, and for the hylan G-F 20 + NSAID group, statistically significant superiority over the NSAID-only group was

Table IV
Mean visual analog scale scores at week 26 assessed by the follow-up telephone interview at week 26. The values are the means of the visual analog scale scores ± S.E.

Outcome measure	NSAID ($N=31$)	Hylan G-F 20 ($N=27$)	Hylan G-F 20+ NSAID ($N=32$)
Pain with motion	52 ± 4*	40 ± 5	37 ± 4*
Pain at rest	22 ± 3*	25 ± 3†	11 ± 3*†
Pain at night	28 ± 4*	25 ± 5†	9 ± 4*†
Restriction of activity	52 ± 5*	41 ± 5	38 ± 4
Overall assessment of arthritic pain	52 ± 4*	47 ± 4	37 ± 4

*Indicates that the hylan G-F20 + non-steroidal anti-inflammatory drug (NSAID) group was statistically significantly superior ($P < 0.05$) to the NSAID-only group in all the variables.
†Indicates where comparisons between the hylan G-F 20 + NSAID group and the hylan G-F 20-only group were statistically significantly different ($P < 0.05$), i.e. pain at rest and pain at night.

Table V

Patients who were 'symptom-free' at the week 26 follow-up telephone interview. Symptom-free was defined as a reduction of the patient's visual analog scale score to <20 mm

Outcome measure	NSAID-only *N* (%)	Hylan G-F 20-only *N* (%)	Hylan G-F 20 + NSAID *N* (%)
Pain with motion	2 (6%)*†	8 (30%)*	9 (28%)†
Pain at rest	15 (48%)†	13 (48%)‡	26 (81%)†‡
Pain at night	15 (48%)†	17 (63%)	25 (81%)†
Restriction of activity	3 (10%)	7 (26%)	8 (25%)
Overall assessment of athritic pain	3 (10%)	5 (19%)	8 (25%)

*Indicates where comparisons between the hylan G-F 20-only group and the non-steriodal anti-inflammatory drug (NSAID)-only were statistically significantly different ($P < 0.05$).
†Indicates where comparisons between hylan G-F 20 + NSAID group and the NSAID-only group were statistically significantly different ($P < 0.05$).
‡Indicates where comparisons between the hylan G-F 20 + NSAID group and the hylan G-F 20-only group were statistically significantly different ($P < 0.05$).

found for every evaluation variable. Thus, when pain is measured 6 months after hylan G-F 20 administration, the efficacy of viscosupplementation with continuous NSAID therapy is statistically significantly better for variables which did not show any difference at 12 weeks. Rest pain and night pain in the hylan G-F 20 + NSAID group were also significantly improved when compared to the hylan G-F 20-only group at week 26. These data suggest a long-term additive value for hylan G-F 20 viscosupplementation when combined with NSAID therapy.

Table V presents a categorical analysis of the percentage of patients in each treatment group whose VAS scores were reduced to <20 mm, which was defined as a 'symptom free' score. Again the two hylan G-F 20 groups consistently did better than the NSAID-only group, with pain with motion in the hylan G-F 20-only group being significantly better, and pain with motion, pain at night and rest pain significantly better in the hylan G-F 20 + NSAID group.

Fifteen patients in the hylan G-F 20-only group resumed taking their NSAID at some point between weeks 12 and 26, and 12 were able to refrain completely from NSAID use (Table VI). The protocol did not specifically instruct the patients with respect to NSAID therapy after the last study visit (week 12). These two subgroups of the hylan G-F 20-only group were separately evaluated and compared. The hylan G-F 20-only patients who took no NSAIDs for the entire 26-week period were called 'hylan G-F 20-only-26', and the hylan G-F 20-only patients who resumed NSAID use between weeks 12 and 26 were called 'hylan G-F 20-only-12'.

The 12 'hylan G-F 20-only-26' patients, i.e. those who were able to refrain completely from NSAID therapy for the full 26-week period, had consistently better scores than did the 15 'hylan G-F 20-only-12'

Table VI

Outcome measures for the hylan G-F 20-only group—comparison between those who did or did not resume use of non-steriodal anti-inflammatory drugs (NSAIDs) between weeks 12 and 26. The mean visual analog scale measures ± S.E. for the outcome measures assessed at the 26 week follow-up telephone interview for the patients who were randomized to the hylan G-F 20-only group, comparing the patients who resumed using an NSAID with those who did not

	Mean ± S.E.		
Variables	Hylan G-F 20-only-12 ($N=15$)	Hylan G-F 20-only-26 ($N=12$)	*P*-value
Pain with motion	56 ± 5	21 ± 5	0.0001
Pain at rest	30 ± 5	19 ± 6	NS
Pain at night	31 ± 8	17 ± 9	NS
Restriction of activity	53 ± 6	25 ± 6	0.0029
Overall pain	55 ± 6	37 ± 7	0.0468

The 'hylan G-F 20-only-12' subset is the patients in the hylan G-F 20-only group who resumed NSAID therapy between weeks 12 and 26. The 'hylan G-F 20-only-26' subset is the patients in the G-F 20-only group who did not resume NSAID therapy between weeks 12 and 26.

patients, i.e. those who resumed NSAID use. For three of the five pain variables this difference was statistically significant despite the small group size (Table VI). Although this observation probably results, at least in part, from the fact that patients who resumed NSAIDs did so because they were experiencing increased pain, nevertheless 44% of the patients in the hylan G-F 20-only group were sufficiently improved for 6 months to refrain completely from taking NSAIDs, and many were improved to a level that they would be classified as 'symptom-free' (<20 on VAS).

SAFETY

Sixty-eight patients in the 'intent-to-treat' patient population received a total of 238 hylan G-F 20 injections (with or without NSAIDs). One patient received a single injection, 55 received three injections and 12 received six injections. Adverse events were reported in the case report forms of only six patients. Three of these were unrelated to hylan G-F 20 injections: one patient was in the NSAID-only group, one patient had an accident-related lower back sprain and one patient had a whiplash resulting from an automobile accident. The remaining three patients had local and transient adverse events in the injected knees; only one resulted in withdrawal from study.

Two of the three local reactions observed after intra-articular injection of hylan G-F 20 that were attributable to the device were similar in their clinical presentation. Pain began within 24 h after injection, accompanied by warmth and effusion. The effusion was removed by arthrocentesis and analyzed for cells, crystals and microbiology. One of the synovial fluids was reported to have a high macrophage count, but they were otherwise unremarkable. Both patients recovered within several days without sequelae. The third adverse event was not reported until several months after the injections were completed and the temporal relationship between the injection and the onset of pain was not clear. The patient continued to receive intra-articular hylan G-F 20 and no effusion could be collected during the arthrocenteses that preceded each subsequent two injections. Despite the patient's reported increase in pain, his VAS scores for pain decreased over the course of the three hylan G-F 20 injections.

Discussion

This clinical trial was designed to provide practical information on how hylan G-F 20 viscosupplementation fits into the medical armamentarium for treating OA of the knee. It addresses the clinically relevant question of how to treat patients with OA on NSAID therapy who are not achieving sufficient pain reduction. Furthermore, the study design enabled an evaluation of whether hylan G-F 20 viscosupplementation can prevent a flare in pain when NSAID therapy was discontinued. For these reasons the study was designed without a wash-out period and without a placebo control. The three study groups enable a direct comparison of patients on NSAIDs who either: (1) continue their medication; (2) discontinue their medication and replace it with three hylan G-F 20 injections; or (3) continue their medication and add three hylan G-F 20 injections to their therapeutic regimen. Patients in all three groups received arthrocenteses in order to control for the intra-articular injection and to maintain blindness.

The results of this study support the hypothesis that treatment of the pain of OA of the knee with hylan G-F 20 is at least as effective as treatment with NSAIDs. Furthermore, the patients discontinued from NSAIDs did not flare when they were treated with hylan G-F 20 viscosupplementation. The patients improved with all treatments, but among their responses only a few of the differences were statistically significant, all in favor of hylan G-F 20, but these differences were of small magnitude and would not likely be clinically meaningful. The question of whether or not a significant difference was missed (type II error) was addressed by analyzing the data for equivalence. The result of this analysis showed that the response with hylan G-F 20 alone was, at the 95% confidence level, *at least* 60% as efficacious as that of the NSAID-treated groups. This is the level that is conventionally accepted as indicating pharmaceutical equivalence [34].

It is interesting to note that there was an increased response to NSAIDs, despite the absence of a wash-out phase. Several factors may contribute to this response. First, participation in the trial itself may have a placebo effect. Second, the patients may also have responded to arthrocentesis. Finally, these improvements may also reflect the natural cycle of flare and remission that characterizes pain of OA. However, irrespective of the cause, there is no reason to suspect that the response was due to a factor that differs among the treatment groups.

The study was not designed to and cannot answer the question of whether or not there was a synergistic effect. If there were, the magnitude would have to be small. Likewise, there is no suggestion whatsoever of any antagonistic influences between hylan G-F 20 and NSAIDs.

Data obtained by telephone interview 26 weeks after the three hylan G-F 20 injections demonstrate some statistically significant differences between these three alternative treatments. The hylan G-F 20 and NSAID group showed significantly less pain than the NSAID-only group for all of the key outcome measures. Even the hylan G-F 20-only group showed significantly less pain on motion when the week 26 data were analyzed categorically (data not shown). Thus, there appear to be some benefits emerging 6 months after patients are treated with hylan G-F 20, despite their being little if any measurable benefit over NSAID therapy at 3 months after hylan G-F 20 injection.

One of the most important aspects of viscosupplementation compared with therapy with analgesics or NSAIDs is that its analgesic effect lasts for months after the intra-articularly injected viscosupplementation product has cleared the joint and the body. Studies on animals and humans clearly showed that injected exogenous hyaluronan and hylan G-F 20 is completely removed from the joint and the body within 7–14 days [38, 39]. Yet, as this study showed, 44% of the hylan G-F 20-only treated patients showed significant improvement after 6 months, without any concomitant therapeutic intervention.

The indication for treatment with hylan G-F 20 is to relieve the pain of OA of the knee and in that it was shown to be as effective as continuous NSAID therapy. This trial, in the time frame of the 12 weeks of the study and the 26 week follow-up, can not, of course, address the issues of 'chondroprotection' or 'chondrodestruction', i.e. whether or not the treatment affects the rate of change in the structural deterioration of the joint. Nevertheless, if the pain relief afforded by the therapy allows normal, but not excessive, joint use, one might expect at least a beneficial physiological response. It could also confer extra benefit to the patient by allowing constitutional exercise without gastric, hepatic and renal toxicity, or other systemic side-effects of the NSAIDs.

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