A Randomized, Single-Blind Comparison of the Efficacy and Tolerability of Hylan G-F 20 and Triamcinolone Hexacetonide in Patients with Osteoarthritis of the Knee

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ABSTRACT. ***Objective.*** To assess prospectively the efficacy and tolerability of hylan G-F 20 (HG-F 20; Synvisc®) and intraarticular triamcinolone hexacetonide (TH; Aristospan®) for treatment of osteoarthritis (OA) knee pain in a 26 week, randomized, multicenter, evaluator-blind study.

Methods. Patients with OA were treated with typical regimens of HG-F 20 (n = 113) and TH (n = 102). Primary assessments were the WOMAC question A1 (pain walking on flat surface), and a 100 mm visual analog scale (VAS) for patient and investigator overall assessments. Total WOMAC and WOMAC domain C (function) scores were also assessed. The intent-to-treat population was analyzed using a last-observation carried forward approach.

Results. Maximum pain relief occurred at 1–2 weeks for TH and at Week 12 for HG-F 20. At Weeks 12 and 26, HG-F 20 was significantly better than TH for the WOMAC question A1 responses ($p = 0.0071$ and $p = 0.0129$, respectively), and patient VAS ($p < 0.0001$ and $p < 0.0001$) and investigator VAS ($p < 0.0300$ and $p = 0.0004$) assessments. Similar significant ($p < 0.01$) results were observed at Weeks 12 and 26 for total WOMAC and domain C scores. While 15 TH-treated patients discontinued the study due to lack of efficacy, none did so with HG-F 20 treatment ($p < 0.01$). Both agents were well tolerated with similar adverse event profiles.

Conclusion. Viscosupplementation with HG-F 20 resulted in a longer duration of effect than TH with a comparable tolerability profile. These data support the preferential use of HG-F 20 over TH for treatment of chronic OA knee pain. (J Rheumatol 2004;31:333–43)

Key Indexing Terms:
HYALURONIC ACID HYALURONAN HYLAN G-F 20 OSTEOARTHRITIS
CORTICOSTEROIDS TRIAMCINOLONE HEXACETONIDE

Osteoarthritis (OA) of the knee is characterized by chronic pain, cartilage matrix degradation, deterioration of the mechanical properties of the synovial fluid, bony osteophyte formation, and episodic inflammation. Compared to healthy joints, the synovial fluid in joints affected by OA can be characterized by both diminished molecular weight and concentration of its primary functional constituent, hyaluronan[1]. Hyaluronan is a polysaccharide consisting of repeating linear dimers of N-acetylglucosamine and glucuronic acid. It is physiologically ubiquitous in the animal kingdom, in particular existing as a large molecular weight substance in bony joints where small quantities serve as both a lubricant and a transport medium for nutrients, proteins, and degradation products related to joint tissue metabolism. Lower molecular weight hyaluronan found in osteoarthritic joints fails to retain its viscoelasticity and ability to withstand shear forces, both small (normal joint movement) and large (high impact forces). As a result, joint surfaces can become progressively damaged when endogenous hyaluronan production is reduced by disease.

Treatment of OA remains a significant clinical challenge. OA is a highly prevalent, age-associated disease that often results in dramatic life-style changes and burdensome economic and social costs. Effective treatment remains elusive, as it hinges on the development of a more precise understanding of the degenerative processes. Putative mechanisms by which hyaluronan injections may exert their clinical effects are suggested by animal models and preclinical

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studies and include preserving cartilage[2-7], as well as modulating proinflammatory cytokines, and matrix metalloproteinases and their inhibitors[8-10]. The mechanism of action of hyaluronan products in humans has not been established; however, a combination of factors has been proposed including restoration of joint rheology, antinociceptive effects, antiinflammatory effects[11,12], and normalization of endogenous hyaluronan synthesis[13]. Some clinical studies also suggest cartilage effects[14-16]. Corticosteroids may work through influencing levels of collagenase and aggrecan[17], as well as matrix metalloproteinases and proinflammatory cytokines[18,19].

Viscosupplementation with hyaluronan and its derivatives helps to replace failing arthritic synovial fluid. Hylan G-F 20 (Synvisc®) is a high molecular weight, cross-linked derivative of hyaluronan formulated as an elastoviscous fluid. The clinical benefits of hylan G-F 20 can persist well beyond its intraarticular (IA) residence time and are thought to be the result of the reestablishment of joint homeostasis[1]. Hylan G-F 20 is presently indicated for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative, nonpharmacologic therapy and simple analgesics (e.g., acetaminophen)[20]. The product information for hylan G-F 20 indicates that a maximal therapeutic effect is achieved at 8 to 12 weeks, with efficacy lasting up to 6 months[21-23].

Generally, IA corticosteroid injections are used intermittently in the treatment of OA symptoms. While recognized as primarily antiinflammatory agents, corticosteroids are occasionally used in the absence of severe inflammation in patients who have pain despite the use of other treatments and who are unsuitable for surgical intervention. Human data to support the use of corticosteroids for these indications are inconsistent. Corticosteroids are generally believed to have a short duration of efficacy, and the clinical data that do exist tend to support this[24-26]. Repeated injections of corticosteroids may hasten the deterioration of articular cartilage and thus accelerate OA damage[27,28]. For this reason, it has been recommended that IA corticosteroids be administered no more than 3 to 4 times annually[29]. Triamcinolone hexacetonide (TH) suspension (Aristospan®) is a relatively long-acting corticosteroid commonly used for IA injections. Corticosteroids have been used to treat conditions such as, but not limited to, inflammatory arthritis (e.g., adult and juvenile rheumatoid arthritis or crystal-induced arthritis), OA of the knee and other joints, bursitis, epicondylitis, and tenosynovitis[26].

In this prospective study we evaluated the efficacy and tolerability of a single course of hylan G-F 20 compared with a typical course of treatment with IA TH. The goal was to determine whether hylan G-F 20 is more efficacious and provides a more durable beneficial response to OA knee pain than corticosteroids. Such findings would support that hylan G-F 20 is more appropriate for many OA patients with chronic knee pain who currently receive corticosteroids.

MATERIALS AND METHODS

This study was conducted in accord with the principles of Good Clinical Practices of the US Food and Drug Administration and with the International Conference on Harmonization guidelines. The study protocol and patient informed consent form were reviewed and approved by the investigators' institutional review boards.

Patient selection. Patients were ambulatory men and women, 40 years of age or older, in generally good health, who had been diagnosed with OA of the knee (criteria of the American College of Rheumatology[30]) at least 3 months prior to entering the study, and had given informed consent to participate. Patients were required to have been taking analgesics/nonsteroidal antiinflammatory drugs (NSAID) to control OA knee pain at least 3 days per week for a minimum of 2 months before enrollment, and have a score ≥ 2 on Question A1 of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at screening, 14 days prior to starting therapy. They also needed to have a score of 50 to 90 mm on a 100 mm visual analog scale (VAS) for both patient and investigator overall assessments of the target knee at baseline. Women of child-bearing potential were required to be using adequate means of contraception. Patients were excluded from entering the study on the basis of having any unstable medical condition, or any of the following diagnoses: acute synovitis, allergy to avian products/hyaluronan-based injection components/corticosteroid injections/acetaminophen, inflammatory arthropathy or infection in the area of the injection site, a clinical diagnosis of primarily patellofemoral knee pain, effusion of > 10 ml at screening or baseline, venous or lymphatic stasis in the leg, claudication or peripheral vascular disease, malignancy within 5 years, diabetic neuropathy or related infections, and laboratory abnormalities. The use of glucosamine and/or chondroitin sulfate was prohibited. Patients were not to have been exposed to prior viscosupplementation in the target knee, oral corticosteroids, or IA corticosteroid injection of a target knee within 3 months of screening or a nontarget joint within 4 weeks. Longer-acting analgesics and NSAID (e.g., rofecoxib) were to be discontinued at least 7 days before baseline and could not be used during the study. Patients with a history of target joint arthroplasty were not permitted to participate in the study. Patients were permitted to use medications for preexisting conditions. Except for within 24 h of a study visit, the following oral pain medications were allowed: acetaminophen (up to 4000 mg/day); analgesics or short-acting NSAID with a washout of at least 24 h (according to product labeling) for pain other than in the target knee, but not for more than 3 consecutive days or 10 days per month; and low dose aspirin (≤ 325 mg/day) for antithrombotic prophylaxis. NSAID with once-daily dose regimens were prohibited.

Test materials. The study injections investigated were the commercially available hylan G-F 20 (Synvisc®) and TH (Aristospan®). Typical regimens for each study treatment were given. Hylan G-F 20 was given as three 2 ml IA injections, at one week intervals. TH was given as a single IA injection of 40 mg[31,32] (2 ml of a 20 mg/ml suspension). Aseptic techniques were rigorously followed. Injections were made using an 18 to 22 gauge needle. Injection approach to the knee was left up to investigator discretion. Preadministration of anesthetic skin spray or subcutaneous local anesthetics was permitted. If effusions were present, they were aspirated and assessed for infection or crystals. Mixing of other agents (including local anesthetics) with IA study injections was forbidden.

Study design. This study was a prospective, multicenter, randomized, single-blind, parallel-group clinical trial. The clinical observer (evaluating physician) was blinded to the therapy received. The goal was to compare the efficacy and tolerability of a course of hylan G-F 20 therapy to a typical course of TH therapy. The patients, dispensers, and injecting physicians were instructed to maintain blinding to ensure the integrity of the study.

Patient visits occurred at Weeks –2 (screening), 0 (baseline), 1, 2, 4, 8, 12, and 26. At screening (Week –2), patient medical history was taken, a complete physical examination (including laboratory assessments) performed, the target knee examined, and a radiograph of the target knee taken. At baseline (Week 0), within 14 days of screening, eligible patients

were randomized to and administered study injection. At Weeks 1 and 2, hylan G-F 20 patients received their second and third injections, respectively, while the TH patients received no additional treatment. Study injections were performed by a clinician other than the observer. The observer remained blinded throughout the study. Efficacy measures (WOMAC and VAS) were assessed (prior to any injection) at all visits from screening and baseline to Week 26. Adverse events were evaluated at baseline and at all visits from Week 1 through 26. Laboratory evaluations and complete physical examinations, including weight and vital signs, were performed at baseline and at Weeks 12 and 26.

Efficacy measures. The primary outcome measures were Question A1 of the WOMAC (pain while walking on a flat surface) and VAS scores for patient and investigator (blinded observer) overall assessments. The WOMAC is a highly reliable, fully validated instrument for assessment of changes in OA symptoms and disability that has been used for 20 years[33,34]. Studies have shown the sensitivity of this instrument to improvements in OA knee pain brought about by treatment with hylan G-F 20[35]. The WOMAC instrument consists of 3 sections or domains. Domain A is a 5-question assessment (A1 through A5) of OA pain. Domain B consists of 2 questions that assess the degree of joint stiffness; and domain C is a 17-question assessment of the effects of OA on a patient's physical function. Each question is measured on a 5 point categorical scale (0 = none to 4 = extreme). Maximum possible scores for the WOMAC A, B, and C domains are 20, 8, and 68, respectively, with a maximum possible total WOMAC score of 96. In general, an improvement of 20% from baseline is considered to represent a clinically meaningful change for the WOMAC instrument[36]. Patient and investigator (blinded observer) overall assessments were each measured as a single question using a 100 mm VAS scale.

Secondary outcomes were the overall (total) WOMAC score, the WOMAC domain C (function) score, use of analgesics, the rate of early withdrawals, and an analysis of responder rate.

Three patient cohorts were analyzed; safety, intent-to-treat (ITT), and valid for efficacy (VFE). The safety population included all patients who received at least one study injection. The ITT population included all patients who received at least one study injection and who had at least one efficacy measurement before and after that injection. The VFE population included those patients who received all treatment injections (3 for the hylan G-F 20 group and one for the TH group), completed all single-blind assessments in the visits in which study injections were administered, and had no major protocol violations. Whereas the ITT population was the basis for analysis of the primary efficacy variables, the VFE population served as a means to confirm the ITT analysis.

Tolerability assessment. Adverse events were defined as any untoward, undesired, or unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations that occurred during the study, regardless of the causal relationship to the study treatment. Adverse events were recorded based on the signs and/or symptoms detected during physical examination and clinical evaluation of the patient. In addition, the patient was asked the nonspecific question, "How have you been feeling since your last visit?" Investigator verbatim terms for adverse events were coded into terms of the *Medical Dictionary for Regulatory Activities* (MedDRA). Relatedness to study injection (not, possible, probably, or definitely) and severity were assessed by the investigator for all adverse events.

To elucidate the local injection site adverse event profile, the associated site reaction terms coded by MedDRA were analyzed by aggregate terms. The first aggregate term was "injection site-related" events, which included the MedDRA terms bruising, erythema, joint pain, joint swelling, edema, pain, pruritus, and reaction not otherwise specified. The second aggregate term was "swelling-related" events, which included erythema, injection-site erythema, injection-site joint swelling, joint effusion, joint swelling, popliteal bursitis, and swelling not otherwise specified. Analysis of events was per-injection, which helped to control for the more frequent injection schedule associated with hylan G-F 20 when comparing the treatment groups.

To report the incidence of adverse events consistently with that in the hylan G-F 20 product information, investigator verbatim descriptions of study treatment-related local adverse events occurring within 30 days of any study injection were examined. Descriptions were grouped into 2 categories: pain and/or swelling-related events, or events clearly related only to the injection procedure itself. Events that did not fall obviously into one of these 2 groups were not included in the analysis. The events were analyzed on a per-patient basis consistent with the production information. The same patient was counted only once in each category, but could be counted in both categories.

Statistical methods. The sample size estimate was based upon the WOMAC Question A1, making the following assumptions: a between-group effect size of 0.5 at Week 12, a variance estimate of 1, α-error probability of 5%, and power of 80%. A power of 80% required 63 patients per group, while 90% power required 85 patients per group. The primary null hypothesis was that the hylan G-F 20-treated patients would experience the same amount of pain walking on a flat surface as those treated with TH 12 and 26 weeks after treatment. The software used to calculate these sample size estimates was PASS, version 6.

This report is based on 218 randomized patients of the intended total of 220. Following the statistical analysis plan, Weeks 12 and 26 were the only primary efficacy time points that were statistically analyzed. The primary endpoints were assessed using a last-observation carried forward approach on the ITT population. The WOMAC A1 absolute change data were analyzed using analysis of covariance (ANCOVA), with baseline score as a covariate and treatment and center as factors, at Weeks 12 and 26. As the treatment-by-center interaction was not significant for any primary efficacy variable ($p > 0.05$), it was not included in the model. Comparisons between groups for VAS-based overall assessment scores (patient and investigator) were evaluated using the ANCOVA model above with least-square means. Baseline values for primary endpoints were tested using 2-sample t tests.

Secondary efficacy variables were assessed similarly. Total WOMAC and WOMAC domain C scores were evaluated for treatment differences at Weeks 12 and 26 using ANCOVA, with baseline score as a covariate and treatment and center as factors. As the treatment-by-center interaction was not significant for any secondary efficacy variable ($p > 0.05$), it was not included in the model. The frequency of patients using analgesics was presented as the number and percentage of users for each visit interval. The distribution of number of days to dropout was estimated with Kaplan-Meier methods. An analysis of the per-visit percentage of responders was performed at all time points. For purposes of analysis, a responder was a patient who had improved from baseline by at least one point on WOMAC Question A1 at a given visit.

Adverse events were listed and analyzed by body system and primary MedDRA term, as were those adverse events related to the target knee. Specific aggregate terms (noted above) were created to assess local injection site-related events and swelling events. Fisher's exact test was used for comparisons of frequencies of individual and aggregate events.

RESULTS

Patient demographics and disposition. Demographic details for the safety population of each treatment group are presented in Table 1. There were no statistically significant or clinically relevant differences in demographic characteristics between the treatment groups. Overall, the mean age of the population was 63.1 years, with more women than men (123 women, 93 men) and the majority of patients Caucasian (85%). Patients over 64 years of age represented 42% of the population in both treatment groups. The population was of average height and weighed slightly more than predicted normal (mean height 66.9 in; mean weight 198.7 lbs; mean body mass index 30.95 kg/m^2). Importantly, the

Table 1. Patient characteristics.

Characteristic	Hylan G-F 20, n = 113	TH, n = 103	p*
Age, yrs, mean ± SD	62.5 ± 12.1	63.7 ± 11.6	0.445
Height, in	66.7 ± 4.1	67.1 ± 4.2	0.513
Weight, lbs	197.1 ± 46.9	200.5 ± 39.7	0.569
Body mass index, kg/m^2	30.8 ± 6.7	31.1 ± 6.0	0.732
M:F	46:67	47:56	0.465
Ethnicity, n (%)			0.552
Caucasian	99 (88)	84 (82)	
African American	7 (6)	12 (12)	
Hispanic	6 (5)	6 (6)	
Others	1 (1)	1 (1)	
Target knee, R:L	54:59	52:51	0.692
Radiologic severity, n (%)			0.252†
Doubtful	0 (0)	2 (2)	
Minimal	17 (15)	9 (9)	
Moderate	64 (57)	64 (62)	
Severe	32 (28)	28 (27)	

* Quantitative variables assessed by t test; † categorical variables by chi-square test. Safety population: all patients who received at least one study injection; TH: triamcinolone hexacetonide.

distributions of target knee radiologic disease severity were balanced between treatment groups at baseline.

Baseline measures for all efficacy variables are provided in Table 2. As shown by the absence of statistical significance between the treatment groups, patients in both groups presented with comparable symptoms and disability at study entry.

A summary of patient disposition, including the number of patients in each analysis cohort, is provided in Table 3. Of the 218 patients randomized, there were 216 in the safety population, 215 in the ITT population, and 177 in the VFE population. For the purposes of statistical and scientific rigor, the results of the analysis for the ITT population are described here. However, in general, results for the VFE population were similar to those obtained from the ITT analysis.

A total of 83 (74%) and 70 (67%) in the hylan G-F 20 and TH groups, respectively, completed the 26-week study period. Patients' reasons for early discontinuation are given in Table 3. The 3 most common reasons for discontinuation were occurrence of adverse events, unsatisfactory efficacy response, and lost to followup. The proportion of patients in each treatment group discontinuing as a result of an unsatisfactory efficacy response was 14% in the TH group compared to none in the hylan G-F 20 group (p = 0.001, Fisher's exact test). When patient discontinuation was examined prior to Week 4, the main reason patients in the TH group dropped out was lack of efficacy, followed by

Table 2. Baseline values for primary and secondary efficacy variables. Data are mean ± SEM unless stated otherwise.

Efficacy Variable (units)	Hylan G-F 20, n = 113	TH, n = 102	p*
WOMAC domain A Question 1 (0–4)			
Total score	2.12 ± 0.07	2.15 ± 0.07	0.743
Categories, n (%)			
0 (none)	1 (1)	0 (0)	
1 (mild)	18 (16)	14 (14)	
2 (moderate)	66 (58)	61 (60)	
3 (severe)	23 (20)	25 (25)	
4 (extreme)	5 (4)	2 (2)	
Patient-assessed VAS score, mm	68.4 ± 1.39	67.3 ± 1.29	0.542
Investigator-assessed VAS score, mm	69.0 ± 1.14	69.6 ± 1.07	0.692
WOMAC domain A score (0–20)	10.7 ± 0.33	10.4 ± 0.30	0.425
WOMAC domain B score (0–8)	4.7 ± 0.13	4.9 ± 0.16	0.584
WOMAC domain C score (0–68)	38.6 ± 1.09	37.9 ± 1.07	0.657
Total WOMAC score (0–96)	54.0 ± 1.48	53.1 ± 1.45	0.653
Patients using analgesic, %	98.2 ± 1.25	97.1 ± 1.68	0.670†

Intent-to-treat population: all patients who received at least one study injection and who had at least one efficacy measure before and after that injection. TH: triamcinolone hexacetonide. * t test. † Chi-square test.

Table 3. Patient disposition.

	Hylan G-F 20, n (%)	TH, n (%)	Total, n (%)
Randomized	113	105*	218
Safety population	113	103	216
ITT population	113	102	215
VFE population	90	87	177
Discontinued study	30 (27)	35 (33)	65 (30)
Reasons for study discontinuation, n (%)			
Adverse event	11 (10)	10 (10)	21 (10)
Unsatisfactory response	0 (0)†	15 (14)	15 (7)
Lost to followup	10 (9)	4 (4)	14 (6)
Patient request‡	6 (5)	0 (0)	6 (3)
Other	2 (2)	3 (3)	5 (2)
Protocol violation	1 (1)	2 (2)	3 (1)
Screen failure	0 (0)	1 (1)	1 (< 1)

* Includes a patient who was mistakenly treated with hylan G-F 20. † Treatment difference favoring hylan G–F 20, p = 0.001, by Fisher's exact test. ‡ Not related to the study. TH: triamcinolone hexacetonide; ITT: intent-to-treat;VFE: valid for efficacy.

other reasons and failure to return. An equal distribution of patients in the hylan G-F 20 group dropped out before Week 4 because of patient request unrelated to the study, failure to return, and other.

Concurrent use of analgesic and antiinflammatory medication by therapeutic class was similar between the treatment groups (Table 4). Additionally, the use of HMG CoA/reductase inhibitors (15% vs 23%; p = 0.1642) and angiotensin-converting enzyme inhibitors (21% vs 18%; p = 0.4975), with or without calcium channel blockers or diuretics, was similar between groups.

Primary efficacy endpoints. Both treatments resulted in significant improvements from baseline in the patients' reported pain due to walking on a flat surface (WOMAC Question A1). In general, beneficial effects appeared to take about a week longer for hylan G-F 20 patients; however, the resulting clinical benefit lasted longer than that reported by patients in the TH group. Mean improvements in WOMAC Question A1 scores are presented in Table 5 and Figure 1. At Weeks 1 and 2, the TH-mediated mean change from baseline scores were greater than those reported in the hylan G-F 20-treated group. By Week 4, the groups showed comparable improvement, with hylan G-F 20 patients showing increasingly greater improvement and TH patients showing a decline in efficacy after the Week 2 time point. At Week 12, hylan G-F 20 patients showed statistically greater improvement compared to TH patients (p = 0.0071). The Week 26 baseline improvement scores were smaller for both groups; however, the difference between treatment groups continued to be statistically significant (p = 0.0129), favoring hylan G-F 20.

The mean overall VAS assessments reported by both the patient and the investigator were also statistically significant at Week 12 (patient, p < 0.0001; investigator, p < 0.0300) and Week 26 (patient, p < 0.0001; investigator, p = 0.0004), demonstrating greater improvement with hylan G-F 20 treatment (Table 5). The patient's overall assessment VAS scores represent a mean improvement from baseline of 46%

Table 4. Concomitant analgesic and antiinflammatory medication taken by treatment group.

Therapeutic Class	Hylan G-F 20, n = 113	TH, n = 103	p*
Anilides	68 (60.2)	59 (57.3)	0.6803
Antiinflammatory agents, nonsteroidal	1 (0.9)	2 (1.9)	0.6065
Coxibs	18 (15.9)	11 (10.7)	0.3192
Natural opium alkaloids	3 (2.7)	5 (4.9)	0.4830
Opium alkaloids and derivatives	0 (0.0)	4 (3.9)	0.0501
Other analgesics and antipyretics	2 (1.8)	5 (4.9)	0.2621
Other opioids	3 (2.7)	2 (1.9)	1.0000
Propionic acid derivatives	27 (23.9)	31 (30.1)	0.3570
Salicylic acid and derivatives	24 (21.2)	24 (23.3)	0.7453
Total NSAID and analgesics	92 (81.4)	80 (77.7)	0.5044

* Quantitative variables assessed by Fisher's exact test. Safety population: all patients who received at least one study injection; TH: triamcinolone hexacetonide.

Table 5. Mean improvements from baseline in primary efficacy variables at Week 12 and Week 26.

Variable (least-square mean ± SEM)	Hylan G-F 20, n = 113	TH, n = 102	p*
Week 12			
WOMAC question A1 (0–4)	0.9 ± 0.1	0.5 ± 0.1	0.0071
Patient VAS, mm	31.3 ± 2.3	17.4 ± 2.41	< 0.0001
Investigator VAS†, mm	32.0 ± 2.2	25.3 ± 2.3‡	0.0300
Week 26			
WOMAC question A1 (0–4)	0.7 ± 0.1	0.4 ± 0.1	0.0129
Patient VAS, mm	28.0 ± 2.5	12.4 ± 2.6	< 0.0001
Investigator VAS†, mm	30.0 ± 2.3	18.2 ± 2.5‡	0.0004

Intent-to-treat population using the last observation carried forward approach. TH: triamcinolone hexacetonide. * Changes in scores were analyzed using ANCOVA with treatment and center as factors and baseline score of the parameter as a covariate. Least-square means were used for changes in VAS score comparisons between groups. † Assessed by a blinded observer. ‡ n = 101.

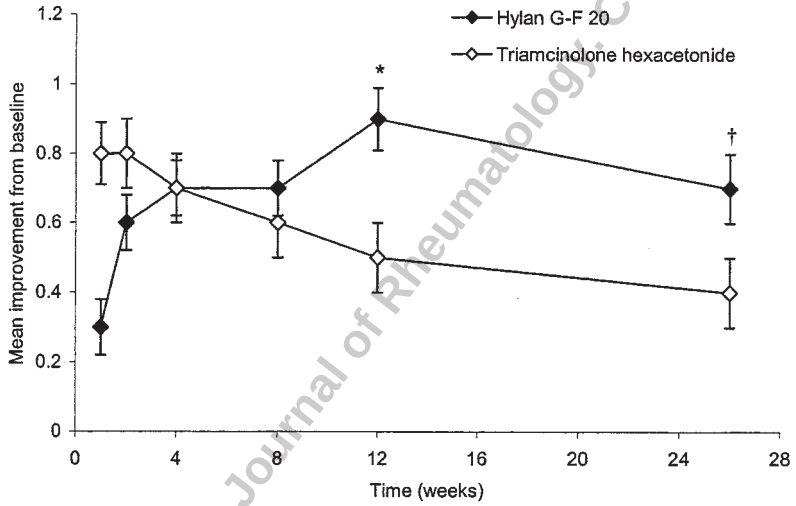

Figure 1. Time course of mean improvements from baseline in WOMAC Question A1 responses with hylan G-F 20 and TH. Mean ± SEM are presented from the intent-to-treat population using the last-observation carried forward approach. Weeks 12 and 26 were analyzed for treatment contrast by ANCOVA, with treatment and center as factors and baseline score as a covariate. *p = 0.0071; †p = 0.0129.

and 41% for the hylan G-F 20 patients' perception of their osteoarthritic condition at Weeks 12 and 26, respectively, compared to 26% and 18% improvements for TH-treated patients.

The statistical analyses of the individual patient shifts in WOMAC Question A1 scores from baseline provided evidence that the time-effect profile to Week 12 and Week 26 was different for the 2 treatment groups (p = 0.006 and p = 0.013, respectively). Hylan G-F 20 treatment resulted in a higher proportion of patients with categorical shifts that reflected pain reduction, e.g., from the categories of moderate or worse at baseline to the categories of mild or no pain by Week 12. At Week 12, 66% of hylan G-F 20-treated patients reported mild or no pain, compared to 47% of TH patients. By Week 26, this effect was slightly reduced (56% and 37% of patients, respectively).

Secondary efficacy endpoints. Secondary efficacy variables indicated that patients in both treatment groups had improved significantly from baseline. By Week 12, there were significant treatment differences reported for the overall WOMAC score (p = 0.0004) and for the WOMAC domain C (p = 0.0006), with patients in the hylan G-F 20 group experiencing greater improvements in their overall OA condition and in their ability to function day to day. This effect was sustained at Week 26 (p = 0.0008 and p = 0.0010, respectively; Table 6). Figure 2 provides the time-effect profile for changes in the Total WOMAC scores.

The by-visit responder analysis based on proportions of

Table 6. Mean improvements from baseline in secondary efficacy variables at Weeks 12 and Week 26.

Variable (least-square mean ± SEM)	Hylan G-F 20, n = 113	TH, n = 102	p*
Week 12			
Full WOMAC score (0–96)	20.7 ± 1.6	12.7 ± 1.7	0.0004
WOMAC domain C score (0–68)	14.6 ± 1.1	9.1 ± 1.2	0.0006
Week 26			
Full WOMAC score (0–96)	18.4 ± 1.7	10.4 ± 1.8	0.0008
WOMAC domain C score (0–68)	13.0 ± 1.2	7.5 ± 1.2	0.0010

Intent-to-treat population using the last observation carried forward approach. TH: triamcinolone hexacetonide. * Change in scores between groups was analyzed using ANCOVA with treatment and center as factors, and baseline score of the parameter as a covariate.

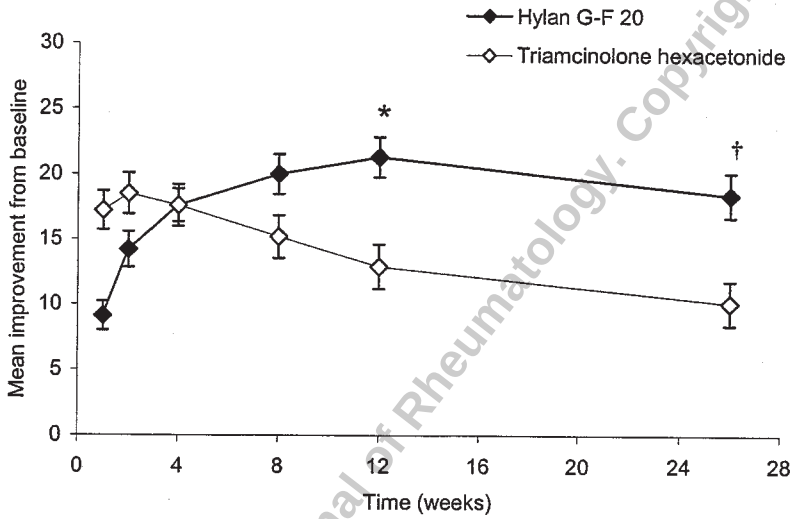

Figure 2. Time course of mean improvements from baseline in total WOMAC responses with hylan G-F 20 and TH. Mean ± SEM are presented from the intent-to-treat population using the last-observation carried forward approach. Weeks 12 and 26 were analyzed for treatment contrast by ANCOVA with treatment and center as factors, and baseline score as a covariate. *p = 0.0004; †p = 0.0008.

patients showing at least a one-point improvement in WOMAC Question A1 is summarized in Figure 3. At Weeks 12 and 26 there were 67 (59%) and 48 (43%) patients with one-point improvements in the hylan G-F 20-treated group compared to 42 (41%) and 30 (29%) in TH-treated patients (p = 0.010 and p = 0.049, respectively).

The probability of patients remaining in the study is presented as a Kaplan-Meier survival curve in Figure 4. These results indicate that the hylan G-F 20-treated patients were more likely to complete the study as intended.

Overall analgesic and NSAID use throughout the study was similar between the hylan G-F 20 (81%) and TH (78%) groups (p = 0.5044). The proportion of patients who used oral analgesics between Weeks 0 and 12 and between Weeks 12 and 26 was similar in both treatment groups. In the hylan G-F 20 and TH groups, respectively, a total of 98% and 97% of patients reported oral analgesic usage up to Week 12 (p = 0.6699). Usage decreased, but remained similar between groups (p = 0.2197), between Weeks 12 and 26 with only 53% and 63% of patients reporting analgesic use in the hylan G-F 20 and TH-treated groups, respectively. Because analgesic use was relatively well balanced and statistically similar between the 2 treatment groups, the contribution of the allowed oral analgesic to the outcome of the study was not assessed further.

Tolerability assessment. No statistically significant differences were observed between treatment groups for the overall incidence of adverse events or the incidence of any single adverse event. The percentage of patients who experienced at least one adverse event, regardless of location, body system, or relationship to study injection, was similar (p = 0.280) between hylan G-F 20 (77%) and TH (70%) groups. The majority of adverse events reported were not considered to be related to the study treatments. Adverse events occurring near the injection site were more likely to be assessed by the investigator as possibly, probably, or defi-

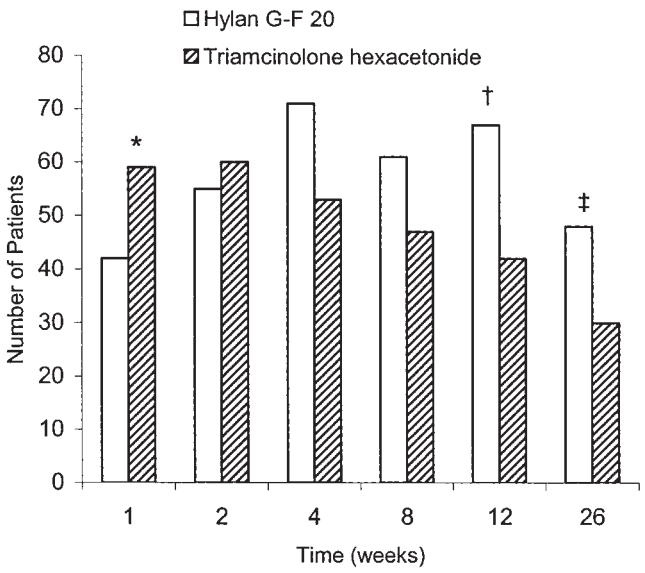

Figure 3. Number of patients with at least a one-category improvement in the WOMAC Question A1 with hylan G-F 20 or TH. Data from the intent-to-treat population are shown. *p = 0.003; †p = 0.010; ‡p = 0.049.

nitely related to treatment. The most frequently reported adverse events (> 5% incidence), regardless of relationship to treatment, are presented in Table 7. Verbatim complaints that coded to local "arthralgia" were the most commonly reported by both hylan G-F 20 and TH patients, and were not significantly different between groups (p = 1.000). The number and severity of local injection-site reactions were also comparable between treatment groups.

Analyzing local injection-site adverse events by aggregate terms, there were no statistically significant differences between the treatments for injection site-related events or swelling-related events following a given injection. Injection site-related events occurred with 7% of hylan G-F 20 and 10% of TH injections (p = 0.224), while swelling-related events occurred with 8% of hylan G-F 20 and 12% of TH injections (p = 0.136).

When treatment-related adverse events were examined using investigator verbatim descriptions consistent with those in the product information, pain and/or swelling-related events were similar (p = 0.220) between treatment groups: 21% of hylan G-F 20-treated patients and 14% of TH-treated patients. Injection procedure-related events were reported by 12% and 7% of the hylan G-F 20 and TH patients, respectively (p = 0.178).

Adverse events accounted for 10% (n = 11) and 10% (n = 10) of study discontinuations from the hylan G-F 20 and TH treatment groups, respectively. Nine serious adverse events in 6 patients were reported during the study, all occurring in TH-treated patients. These events were considered to be not related to treatment and/or were consistent with the age profile of the patient population and the duration of study followup.

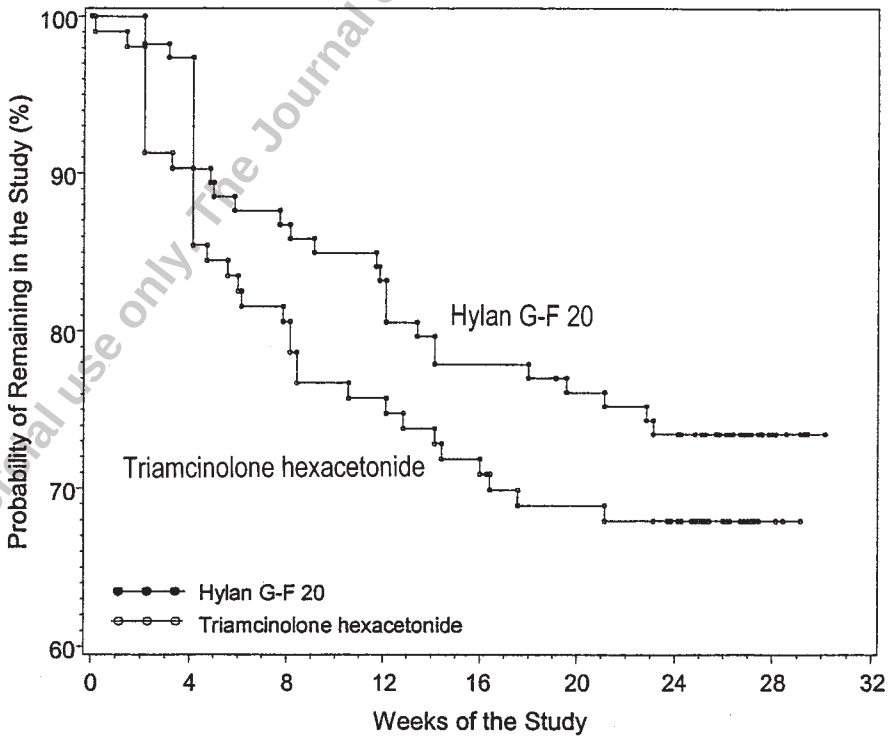

Figure 4. Kaplan-Meier analysis for the probability of patients remaining in the study for each treatment group. Data from the intent-to-treat population are shown.

Table 7. Adverse events reported in ≥ 5% of patients treated with hylan G-F 20 or triamcinolone hexacetonide (TH). When coding events by the term "arthralgia," a relatively large number of disease-related symptoms are included such that all arthralgia-coded events are not necessarily related to the procedure and/or study treatment.

Adverse Event (MedDRA term)	Hylan G-F 20, n (%)	TH, n (%)	p*
Arthralgia	36 (32)	32 (31)	1.000
Headache NOS	13 (12)	7 (7)	0.251
Swelling NOS	9 (8)	5 (5)	0.416
Joint swelling	7 (6)	6 (6)	1.000
Injection site pain	7 (6)	8 (8)	0.790
Joint stiffness	6 (5)	3 (3)	0.503
Injection site swelling	6 (5)	1 (1)	0.122
Injection site edema	5 (4)	7 (7)	0.557
Back pain	3 (3)	6 (6)	0.315
Joint stiffness	6 (5)	3 (3)	0.503

Safety population: all patients who received at least one study injection. NOS: not otherwise specified. * Fisher's exact test.

DISCUSSION

This is the first prospective, randomized, controlled study that compared typical regimens of hylan G-F 20 and IA steroid for the treatment of OA of the knee. It was conducted under observer-blinded conditions in a multicenter setting across the US. The treatment groups were well balanced for baseline demographics and medical condition at study entry. Three weekly IA injections of hylan G-F 20 reduced OA pain of the knee and target joint stiffness, improved function, and improved the overall disease condition. While this was also generally true of triamcinolone hexacetonide, the effect with the intraarticular steroid was of faster onset and reflected a much shorter duration of action and an occasionally smaller magnitude of peak effect. Both treatments had similar tolerability, as shown by the similar incidences and types of all experienced local adverse events.

A clinically relevant mean decrease in the primary endpoint, WOMAC Question A1 (pain while walking on a flat surface), was observed by Week 1 in corticosteroid-treated patients; however, the beneficial effect declined thereafter. In contrast, patients in the viscosupplement-treated group, on average, began experiencing clinically meaningful mean effects in the primary outcome measures by Week 2. These beneficial effects of hylan G-F 20 increased to a maximum by Week 12 and were significantly better than with TH at the study endpoints of Weeks 12 and 26. The statistically significant mean improvement from baseline at Week 12 with hylan G-F 20 compared to TH was maintained at Week 26, as illustrated by similar effect sizes of 0.4 and 0.3 for Weeks 12 and 26, respectively. The pattern of these effects was generally supported by findings for the remaining primary efficacy variables as well as the secondary variables, providing a high degree of internal consistency. Further, the finding that concomitant oral analgesic use was similar between groups lends support to the idea that use of concurrent analgesics did not influence the difference in effect between treatment groups. It was notable, and in keeping with the shorter duration of action of the steroid, that, while a significant number of patients dropped out of the study due to a lack of efficacy, no patient in the hylan G-F 20 group discontinued due to lack of efficacy.

The overall current findings are consistent with previous efficacy reports for both steroid and hyaluronan use. Reports in the literature[24-26] and clinical experience support the observed fast onset of action and short duration of effect with IA corticosteroid. In the only previous double-blind clinical study comparing sodium hyaluronate (Hyalgan®) with triamcinolone, improvement in VAS scores for nominated activity and knee pain at night were consistent with short-term benefit of TH and a longer duration of effect with hyaluronan[37], as observed in our study. A literature review by Creamer shows that of 4 clinical studies involving triamcinolone, all 4 describe some degree of efficacy, contrasted to either placebo (3 studies) or betamethasone (one study), but only for several weeks after drug administration[24]. Creamer's conclusions indicate that further refinement of patient selection is desirable, but that until such progress is made, the use of IA corticosteroids will likely continue when no other effective treatments are available and when clear inflammatory conditions are present.

Similarly, the efficacy results reported here with hylan G-F 20 are similar to a pattern of beneficial effect previously reported. Wobig and colleagues also showed a peak effect of hylan G-F 20 at Week 12 for improvements in both patient and investigator VAS scores for pain during weight-bearing movement of the knee, as well as improvements in VAS scores for loss of activity[22]. Overall, the current data are consistent with previous efficacy results and the product information for hylan G-F 20, which support up to 6 months of clinical improvement after a course of 3 IA injections.

To put these findings into the context of other studies of viscosupplements, it should be noted that diverse study designs, varied endpoints, and dissimilar viscosupplementa-

tion products (various molecular weight hyaluronan species, cross-linked polymers, etc.) have been evaluated over the last 2 decades. These differences in study design may account for the variability observed among studies. The WOMAC instrument is one of the most discerning tools for assessing treatment effects in the study of OA of the knee, as it has been rigorously validated and, as a multidimensional questionnaire, it reflects diverse, important, practical patient outcomes[33,34]. Using the WOMAC instrument, Bellamy, *et al* have shown that improving the clinician's IA injection skills can significantly affect treatment outcome in OA of the knee, as evidenced by the domain A and C scores[38].

Both treatments were generally well tolerated based on the incidences and types of reported adverse events. There were no statistically significant differences in the incidence of any single adverse event in this study, including those that were specifically target knee-related. Importantly, all analyses of adverse events, even the most conservative analysis by investigator verbatim terms, showed no statistically significant differences in the incidence of events between treatment groups. Overall, the types of events seen with the hylan G-F 20 treatment were consistent with previous reports and those events reported in the product information.

In summary, these data demonstrate that intraarticular injection of either hylan G-F 20 or triamcinolone hexacetonide is efficacious in the treatment of OA of the knee. While the onset of action of TH was faster than that of hylan G-F 20, the viscosupplementation therapy resulted in a considerably longer duration of effect than the corticosteroid. The mean improvement from baseline with hylan G-F 20 treatment was significantly better than that with TH at Week 12, and remained significantly greater at Week 26. These findings provide a strong rationale for the preferential use of hylan G-F 20 in patients with chronic knee pain due to OA.

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