Osteoarthritis and Cartilage (2002) **10,** 506–517

1063–4584/02/$35.00/0
doi:10.1053/joca.2002.0798, available online at http://www.idealibrary.com on IDEAL®

Osteoarthritis and Cartilage

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A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results

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Summary

Objective: First, to assess the clinical effectiveness of hylan G-F 20 in an appropriate care treatment regimen (as defined by the American College of Rheumatology (ACR) 1995 guidelines) as measured by validated disease-specific outcomes and health-related quality of life endpoints for patients with osteoarthritis (OA) of the knee. Second, to utilize the measures of effectiveness and costs in an economic evaluation (see accompanying manuscript).

Design: A total of 255 patients with OA of the knee were enrolled by rheumatologists or orthopedic surgeons into a prospective, randomized, open-label, 1-year, multi-centred trial, conducted in Canada. Patients were randomized to 'Appropriate care *with* hylan G-F 20' (AC+H) or 'Appropriate care *without* hylan G-F 20' (AC). Data were collected at clinic visits (baseline, 12 months) and by telephone (1, 2, 4, 6, 8, 10, and 12 months).

Results: The AC+H group was superior to the AC group for all primary (% reduction in mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale: 38% vs 13%, $P=0.0001$) and secondary effectiveness outcome measures. These differences were all statistically significant and exceeded the 20% difference between groups set *a priori* by the investigators as the minimum clinically important difference. Health-related quality of life improvements in the AC+H group were statistically superior for the WOMAC pain, stiffness and physical function (all $P<0.0001$), the SF-36 aggregate physical component ($P<0.0001$) and the Health Utilities Index Mark 3 (HUI3) overall health utility score ($P<0.0001$). Safety (adverse events and patient global assessments of side effects) differences favoured the AC+H group.

Conclusion: The data presented here indicate that the provision to patients with knee OA of viscosupplementation with hylan G-F 20 within an appropriate care treatment regimen provides benefits in the knee, overall health and health related quality of life at reduced levels of co-therapy and systemic adverse reactions.

Key words: Hylan G-F 20, Osteoarthritis, Knee, Effectiveness, Health-related quality of life, Randomized controlled trial.

Abbreviations: ACR, American College of Rheumatology; OA, osteoarthritis; AC+H, Appropriate care *with* hylan G-F 20; AC, Appropriate care *without* hylan G-F 20; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; HUI3, Health Utilities Index; NSAIDS, nonsteroidal anti-inflammatory drugs; FDA, Food and Drug Administration; RCT, randomized controlled trial; CRO, contract research organization; HRQOL, health-related quality of life; SF-36, Short Form 36; ITT, intent-to-treat; ANCOVA, analysis of covariance; GI, gastrointestinal.

Received 4 March 2001; revision requested 10 October 2001; revision received 19 November 2001; accepted 4 February 2002.

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The study was funded by Biomatrix, Inc and Rhône-Poulenc Rorer Canada Inc.

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Introduction

Osteoarthritis (OA) is a common, degenerative musculoskeletal condition which consistently challenges the practising clinician and adds substantial burden to health care budgets[1,2]. The increased prevalence of OA with aging, coupled to the demographics of aging populations, make OA a high priority health care problem[3]. OA is a leading cause of severe activity limitations and disability, with indirect costs to society, which can far exceed its direct medical costs[4].

Guidelines for managing the symptoms of knee OA are available from various sources[5]. The goal of therapy is to control pain and maintain function. Weight control, physical therapy and simple analgesics such as acetaminophen, are suggested as first-line tools for patient management to minimize the need for higher risk treatments such as non-steroidal antiinflammatory drugs (NSAIDs) or surgery. NSAIDs continue to be a widely used medical therapy in response to patient demands for symptomatic improvement. In the United States alone, there are an estimated 56 000 hospitalizations and 8800 deaths each year among OA patients, attributed to NSAID treatment[6].

Viscosupplementation is a new therapy for the treatment of knee OA based on the replacement of synovial fluid by intraarticular injection of viscoelastic solutions containing hyaluronan or its derivatives[7]. Hylan G-F 20 (Synvisc® Genzyme Corporation, Cambridge MA U.S.A.) is one of the viscosupplementation products approved for marketing in Canada since 1992 and the United States since 1997 after public review of the data by a Food and Drug Administration (FDA) advisory panel[8]. A recent systematic review of the randomized controlled trial (RCT) data on viscosupplementation concluded, that despite mixed results, the overall data support the efficacy of viscosupplementation[9]. While some physicians continue to question the efficacy of hylan G-F 20, the reality is that hylan G-F 20 is an approved treatment in Canada, the U.S.A., and most other countries. Furthermore, the recently revised guidelines published by the American College of Rheumatology (ACR) now include viscosupplementation in the treatment paradigm for knee OA, thus establishing it as a standard therapy[10].

Considering the limited resources available for health care, it is important to consider how incorporating the new technology affects patient outcomes and health care expenditures. A randomized, controlled trial of health outcomes was specifically designed to determine the *incremental* effectiveness, cost-effectiveness and cost-utility of making viscosupplementation with hylan G-F 20 available as part of an appropriate care paradigm for treating patients with knee OA. The study utilized a pragmatic design to maintain a real world scenario, and therefore measured effectiveness rather than efficacy[11–14]. That is, rather than asking the question of whether the treatment is efficacious compared to placebo, the trial sought to determine whether the treatment was effective under real world conditions. The Canadian Guidelines for Economic Evaluation of Pharmaceuticals state: 'Ideally, pharmacoeconomic studies should report on drug effectiveness rather than efficacy'[15]. For this reason the trial design minimized protocol-driven interventions and the comparator arm did not include placebo injections. Effectiveness includes all aspects of a treatment that add or detract from its success, including efficacy, patient compliance and satisfaction, safety, and positive or negative interactions with other concurrent treatments.

The availability of a safe and effective local therapy for managing a localized condition such as knee OA might offer important health care benefits. The clinical results and health-related quality of life (HRQOL) outcomes for this trial are reported here, with the economic results separately reported in an accompanying manuscript[16].

Materials and methods

STUDY MANAGEMENT

The study was funded jointly by Biomatrix, Inc and Rhône-Poulenc Rorer Canada Inc. Innovus Research Inc., an independent contract research organization (CRO), was contracted to manage the study. An independent Steering Committee was assembled with the responsibility to design the study, develop the analysis plan, resolve methodological issues that arose throughout the study, and interpret and disseminate study results. The Committee consisted of five academics, one representative from each of the two sponsoring companies and one representative from the CRO. The Steering Committee was deliberately structured to be dominated by the five independent academics on the Committee. The Steering Committee actively dealt with all scientific questions that arose throughout the course of the study, and did so blinded to implications. The contractual arrangement gave the investigators unrestricted rights to publish the study results.

PATIENTS

Patients were enrolled between April and December 1997, at 14 sites across Canada (10 rheumatologists, four orthopedic surgeons). The study protocol and informed consent form were approved by the relevant Ethics Committees for the sites. Informed consent was obtained from each patient.

Patients with age greater than 40 years, were required to have a primary diagnosis of radiologically verified OA in the study knee (knee most symptomatic or with the most predominant musculoskeletal problem), to be symptomatic [visual analogue scale total pain score greater than 175 mm of 500 mm on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale] despite prior treatment with acetaminophen or NSAIDS at any point prior to the study, to be ambulatory and willing to participate and sign informed consent. Patients with Grade IV[17] radiologic changes according to the clinical investigators were excluded. Other exclusion criteria included patients with inflammatory arthropathies, a tense effusion in the study knee at baseline, chondrocalcinosis or those with a severe varus or valgus deformity in the study knee. In addition, patients were excluded if they had received a steroid injection in the study knee during the prior 3 months, if they had prior viscosupplementation therapy, if they had isolated patellofemoral OA or any uncontrolled morbidity, particularly morbidity in any joint which would impede measurements in the study knee.

TRIAL DESIGN

This was a multicentre, 1-year, prospective, randomized, open-label study. Patients were randomized to either 'appropriate care *with* hylan G-F 20' (AC+H) or to 'appropriate care *without* hylan G-F 20' (AC). The AC group only

differed in that intraarticular injections of hylan G-F 20 or other viscosupplementation products were not allowed. Appropriate care was the preferred management strategy of a treating physician who was encouraged to follow the Guidelines for the Medical Management of Osteoarthritis of the Knee proposed by the ACR[5]. Appropriate care could include medications such as analgesics, NSAIDs, corticosteroid injections, supportive measures such as education and counseling, weight loss, joint rest, application of heat or ice, and use of devices, physical therapy, arthroscopy, and total joint replacement.

Hylan G-F 20 is administered as a series of 3 intra-articular injections at intervals of 1 week. The contralateral knee could also be treated with hylan G-F 20, and patients could receive subsequent treatments to either or both knees as required.

Computer-generated randomization was designed to be balanced (1:1 allocation ratio) within each site. Randomization within site was blocked, but the block size was randomly assigned as blocks of 2 or 4, with the additional constraint that blocking was balanced for the first 12 patients. Additional patients exceeding the first block of 12, were randomly allocated in blocks of 2. The allocation scheme was concealed from all clinical sites. Central randomization was used whereby the site telephoned the CRO, provided the patient's initials, and received the patient's identification (ID) number and treatment allocation.

Patients were assessed at the site during the baseline visit and the 12-month termination visit. Patients randomized to AC+H returned to the site for 2 consecutive weeks after baseline for the remaining hylan G-F 20 injections. These were the only site visits required by the protocol. Structured telephone interviews of the patients in both treatment groups were conducted by the CRO at months 1, 2, 4, 6, 8, 10, and 12. The 12-month termination visit was included for patient assessment by the investigator and for measuring change since baseline. Patients returned to the physician as required for clinical deterioration, treatment of adverse events, change in medication, or additional treatment with hylan G-F 20 if required.

Patient demographics, appropriate care treatment for knee OA, treatment for overall OA, concomitant medications, and patient self-administered questionnaires were collected at the baseline visit. The same information was collected during the telephone interviews, with the addition of pill counts performed by the patient, medication dosage and duration, adverse events, health care resources, and whether the health care resource was related to OA. The patients kept a diary to keep track of this information, and their content was provided to the telephone interviewer at each telephone interview. During the telephone interviews, the patient referred to the self-administered questionnaire and provided his/her answers to the telephone interviewer. To blind the patient to his/her previous answers to the same questions, s/he was instructed not to record the answers, and the questionnaire was laminated with plastic to make if difficult if someone tried to do so. Although the questionnaires were completed originally at the baseline visit and then during telephone interviews, a study comparing the completion of the WOMAC Likert 3.0 questionnaire at the physician's office to completion over the telephone found that differences between the modes of administration did not reach statistical significance[18]. Information collected during the telephone interviews (with the exception of the questionnaires) was compared to the patient's medical chart during monitoring visits and differences were resolved. The investigator reviewed the adverse events for possible attribution to study interventions.

OUTCOMES

The primary measure of effectiveness was the mean change in the WOMAC Likert 3.0 pain score in the study knee from baseline to termination. The WOMAC is a self-administered disease-specific HRQOL instrument that asked the patient questions concerning his/her study knee[19]. The WOMAC Likert 3.0 provides scores for three subscales: pain, stiffness, and physical functioning, and an aggregate total score.

There were also measures of secondary effectiveness. Two of the secondary effectiveness measures were the percent of patients improved at termination since baseline using different combinations of the WOMAC Likert 3.0 subscales as follows: (1) at least 20% improvement since baseline in the WOMAC pain score in the study knee; (2) at least 20% improvement since baseline in the WOMAC pain score in the study knee and *either* 20% improvement in function score or stiffness score. A 20% difference between treatment groups for the primary and secondary measures of effectiveness was established a priori by the Steering Committee as the minimum clinically important difference, in part based on previous research[20]. Other secondary effectiveness measures were the patient global assessment of effectiveness for (1) OA in study knee; (2) OA in all joints, and (3) overall health.

HRQOL was measured using three instruments: disease-specific HRQOL using the WOMAC; general HRQOL using the Short Form 36 (SF-36)[21], and preference-based HRQOL using the Health Utilities Index Mark 3 (HUI3)[22]. The SF-36 provides two composite scales: aggregate physical component and aggregate mental component. The HUI3 provides an overall multi-attribute utility score (min: −0.36, death: 0, max: 1). The overall utility score is the preference or worth assigned to a particular health status on an interval scale where 0 represents death and 1 represents perfect health. States worse than death can take on negative scores.

Safety was measured in two ways during the course of the study. The first method was by asking patients to report adverse events during each telephone interview and then having the clinical site review the adverse events. The second method of measuring safety was by asking patients to complete global assessments of side effects. Global assessments were measured in two ways: throughout the study at baseline and at each telephone interview recalling the past 4 weeks; and once during the 12-month termination visit recalling the time period since the baseline visit.

STATISTICS

The sample size was calculated to detect a 20% difference between treatment groups in the primary effectiveness measure. Using a power of 90% and α=0.05, the required sample size was 94 patients per group, for a total of 188 patients. The final total sample size required was 252 patients, to accommodate a 20% predicted dropout rate over 1 year and to accommodate stratification by site (15 sites).

All patients enrolled in the study were included in the intent-to-treat (ITT) group for all analyses. However, if a patient in the AC group violated the protocol by receiving hylan G-F 20 treatment, the patient was treated as a

dropout at that point, and all data collected after that time were not included in the analyses. These patients were classified as crossovers, and their data following the hylan G-F 20 treatment were imputed as was done for all dropouts. This was necessary to ensure the analysis was consistent with a comparison of appropriate care in a world with hylan G-F 20 to appropriate care in a world without hylan G-F 20.

Two models were used for the statistical analyses, and results for the first model are provided. The first model adjusted for design variables (baseline value of the variable being analysed, site, blocking by site, BMI, Baseline WOMAC aggregate score), and the second model adjusted for design variables and potentially clinically important differences (as judged by the clinical principal investigator while blinded to treatment allocation) between the treatment groups at baseline.

An analysis of covariance (ANCOVA) was used for the primary effectiveness analysis and the HRQOL analysis. A generalized linear model was performed for analysis of patients improved. A logistic analysis was undertaken for the patient global assessment of side effects and effectiveness. A nested analysis that incorporates the number of events per patient was used to compare the number of gastrointestinal (GI) adverse events.

The hot deck method[23] was utilized to impute data for the primary and secondary effectiveness of patient improved. Dropout patients were matched with a patient who completed the study. The matched patient was randomly selected from the group of patients who matched the dropout patient on criteria deemed most relevant in predicting primary effectiveness. The Last Observation Carried Forward (LOCF) imputation technique was performed to compare to the hot deck method.

Results

PATIENT CHARACTERISTICS

A total of 255 patients were enrolled, 127 patients randomized to AC+H and 128 to AC (Fig. 1). The central randomization process was audited to ensure that the randomization schedule was implemented properly. There were more dropout patients in the AC group (21) than the AC+H group (3) (P=0.001). Of the 21 patients who dropped out of the AC group, the main two reasons were that the patients wanted hylan G-F 20 (eight patients) and that the patients were unwilling to continue (eight patients). As shown in Fig. 1, eight patients randomized to AC received hylan G-F 20 (protocol violators/crossovers), and one patient in the AC+H group did not receive hylan G-F 20 (protocol violator/crossover). The patient changed their mind after being randomized to receive hylan G-F 20. Eighteen of the 24 patients (75%) who dropped out, did so before Month 4. Of the 24 patients who dropped out, four continued to have data collected during the remainder of the study, however, the data were not used in the analyses. Because these four patients violated the protocol by receiving hylan G-F 20 treatment despite being randomized to AC without hylan G-F 20, their data after the hylan G-F 20 injection were not included in the analyses.

Demographic and OA status data are presented in Table I. Greater than 79% of patients in both groups had received previous acetaminophen and NSAID treatment for OA in their knee(s). Although Grade IV OA in the study knee as determined at the sites by the investigators at enrollment was an exclusion criterion, 20% of patients in the AC+H group and 33% of patients in AC had grade IV OA as subsequently determined by central radiologic grading. Greater than 84% of patients in both groups had OA in the other knee, and greater than 68% of patients in both groups had other joints affected.

KNEE OA TREATMENT

Table II lists knee OA and overall OA treatment. All patients except one in the AC+H group had at least one course of hylan G-F 20 in their study knee, and 53 (42%) had at least 1 course in their other knee. Forty-eight patients (38%) in the AC+H group received a second course in the study knee, three patients (2%) received a third course in their study knee, and 20 patients (16%) received a second course in their other knee (data not shown in Table II). There were more patients in the AC group who reported corticosteroid injection(s) in the study knee (89 vs 18) or the other knee (35 vs 8) (both P<0.0001). There were more corticosteroid injections in the AC group in the study knee (149 vs 27) and the other knee (51 vs 14). There were more patients in the AC group taking NSAIDs for any knee (P=0.0062), and other medications for any knee (P=0.0216). Other medications included medications such as antiinflammatories, neuralgia therapy, opioid analgesics and vitamins. There were seven arthroscopies and four total knee replacements in the AC group compared to one arthroscopy and two total knee replacements in the AC+H group. Despite these reductions in the use of medication for the study knee, there was no significant difference between the groups in the utilization of concomitant medications for overall OA (Table II).

The other treatments, not listed in Table II, that were used most often in both groups were exercise, physiotherapy, walking, water exercises, and assistive devices such as bandages, canes, knee braces, bath bars, and orthotics. There were too many details to provide the other treatments and assistive devices results in Table II. However, the cost results summarized in the accompanying economic manuscript indicate that the annual cost per patient for other therapy was $5 in the AC+H group versus $16 in the AC group. The annual cost per patient for assistive devices was $237 in the AC+H group versus $305 in the AC group[16].

EFFECTIVENESS

Table III provides the primary and secondary effectiveness results. The AC+H group was superior to the AC group for all primary and secondary effectiveness measures. These differences were all statistically significant and exceeded the 20% minimum clinically important difference. The AC+H group experienced a 25% greater improvement in the WOMAC pain score in the study knee from baseline to termination (P=0.0001). The AC+H group had a larger percent of patients who improved by at least 20% (P=0.0001). The primary and secondary effectiveness analyses yielded similar results for model 2 (data not shown). Imputation using LOCF did not change the results. The AC+H group experienced 26% greater improvement in the WOMAC pain score, and a 30% greater improvement in percent of patients who improved by at least 20% in WOMAC pain. The AC+H group also did better on the patient global assessments of effectiveness for OA in the

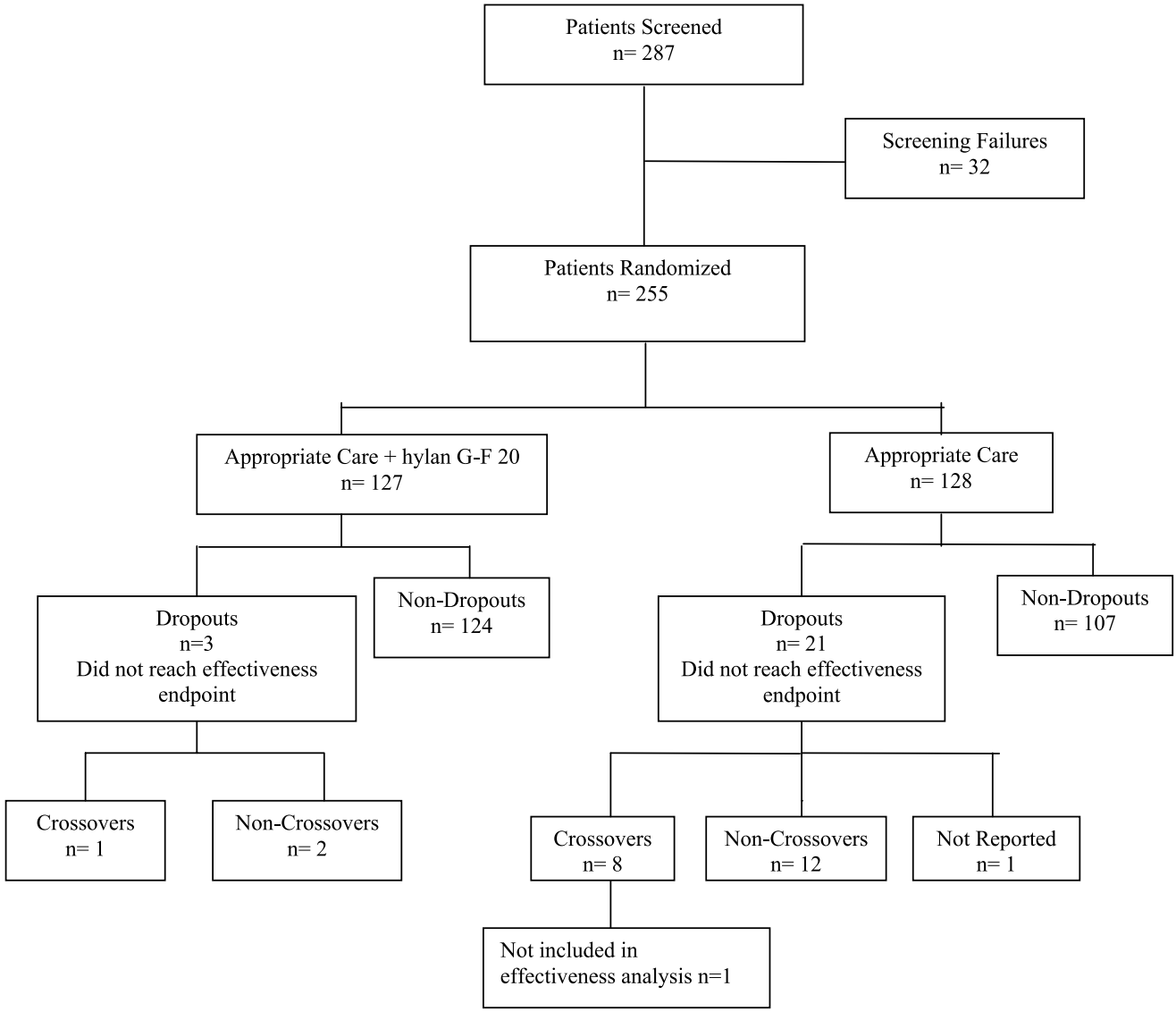

Fig. 1. Trial profile.

study knee, as well as OA in all joints and overall health (P<0.05).

Figure 2 displays the mean WOMAC pain score at each time point during the study year. The patients in the AC+H group had a greater reduction in the WOMAC pain score over the full study year compared to the AC group (P=0.0001).

HEALTH-RELATED QUALITY OF LIFE

Table IV provides the baseline, Month 12, change, and change as a % of baseline for the three HRQOL outcome measures. For all three WOMAC subscales, the SF-36 aggregate physical component, and the HUI3 overall health utility score, the AC+H group was statistically significantly superior (P<0.0001). For all cases in the WOMAC and SF-36, the difference between groups was greater than 20% except for the SF-36 aggregate physical component where the difference between groups was 19%.

SAFETY AND TOLERABILITY

Adverse events were reported by 96% of patients (1114 events) in the AC+H group and 90% of patients (1026) in the AC group (not compared statistically). There was one serious adverse event in the AC group (patient presented to the emergency room with a gastro-duodenal ulcer) listed by the investigator as remotely related to appropriate care.

Intraarticular injection of hylan G-F 20 is occasionally accompanied by pain, swelling, or effusion in the treated knee. A local adverse event was defined during the analysis as any emergent signs or symptoms occurring in the knee. The local adverse events were subdivided into those occurring within 48 hours of a hylan G-F 20 injection and those occurring at any other time. There were 82 local adverse events (in 38 patients) that occurred within 48 hours of a hylan G-F 20 injection in the AC+H group. Of these 82 local adverse events, one was reported as related to osteoarthritis, nine were reported as not related to hylan G-F 20, 15

Table I
Demographic information and osteoarthritis status

Demographics, f (percent of *n*)*	AC+H (*n*=127)	AC (*n*=128)
Age in years, mean (S.D.)	62.6 (9.4)	63.5 (10.5)
Sex		
Female	86 (68%)	93 (73%)
Body mass index (kg/m^2), mean (S.D.)	32.1 (8.0)	32.9 (7.2)
OA status		
Duration (years) of OA symptoms		
Study knee, mean (S.D.)	9.0 (9.5)	9.9 (9.7)
Other knee, mean (S.D.)	7.4 (8.8)	8.3 (9.3)
Previous therapy for OA of the knee(s)		
Acetaminophen	100 (79%)	109 (85%)
NSAIDs	120 (94%)	110 (86%)
Prior surgery, study knee	40 (31%)	39 (30%)
Prior surgery, other knee	27 (21%)	23 (18%)
Radiology grading within 1 year (central grading)		
Not reported	0 (0%)	1 (1%)
Grade 0	4 (3%)	4 (3%)
Grade I	17 (13%)	11 (9%)
Grade II	32 (25%)	33 (26%)
Grade III	49 (39%)	37 (29%)
Grade IV	25 (20%)	42 (33%)
OA at baseline		
Other knee affected	109 (86%)	108 (84%)
Any other joints affected	95 (75%)	87 (68%)
Patient global assessment of OA in study knee at baseline		
Not reported	0 (0%)	1 (1%)
Very good	0 (0%)	0 (0%)
Good	2 (2%)	1 (1%)
Fair	44 (35%)	31 (24%)
Poor	58 (46%)	57 (45%)
Very poor	23 (18%)	38 (30%)
Patients global assessment of OA in all joints at baseline		
Not reported	1 (1%)	2 (2%)
Very good	1 (1%)	2 (2%)
Good	9 (7%)	5 (4%)
Fair	54 (43%)	44 (34%)
Poor	47 (37%)	49 (38%)
Very poor	15 (12%)	26 (20%)
WOMAC pain subscale score (0–20), mean (S.D.)	11.4 (2.7)	11.9 (2.9)

*f is frequency, *n* is sample size. Not all percentages sum to 100 due to rounding.
†Radiology grading is based on central grading, which may have differed from the site investigator's determination for patient eligibility.
OA=osteoarthritis; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; AC+H=Appropriate Care+hylan G-F 20; AC=Appropriate Care.

were reported as remotely, possibly or probably related to hylan G-F 20, and 57 related to the injection procedure.

The occurrence of GI adverse events was lower in the AC+H group for total GI events (109 vs 140 events, P=0.0439), and GI events attributed to AC (25 vs 62 events, P=0.0001), and for total severe GI events (26 vs 53, P=0.0033), and severe GI events attributed to AC (5 vs 22, P=0.0024). Medications taken for side effects of OA treatment were collected. Thirty-nine patients in the AC group were taking medications for the gastrointestinal tract compared to 21 patients in the AC+H group (P=0.0057).

For the global assessments of side effects for the time period since baseline, 62% (79/127) of AC+H patients experienced no side effects compared to 41% (52/128) of AC patients (P=0.0100). The global assessments of side effects (combined mild, moderate or severe) performed at baseline and months 1, 2, 4, 6, 8, 10 and 12 are illustrated in Fig. 3. Fewer patients in the AC+H group (52%; 64/124) experienced side effects at Month 12 than patients in the AC group (68%; 73/107) (P=0.0116).

Discussion

This report details the clinical results of a prospective, randomized, effectiveness/health outcomes trial evaluating the incremental value of making a new treatment modality, viscosupplementation with hylan G-F 20, available for the treatment of patients with knee OA. All of the clinical outcomes measured provided consistent results favoring the group receiving AC+H. The difference between the groups was clinically important and statistically significant using a disease-specific instrument (WOMAC 3.0), a generic HRQOL instrument (SF-36), a preference based HRQOL instrument (HUI3) and global evaluations by the patient of OA in the study knee, overall OA, and overall

Table II
Knee osteoarthritis treatment and overall osteoarthritis treatment

Treatment, f (percent of *n*)*	AC+H (*n*=127)	AC (*n*=128)	*P*-value
Number of patients reporting hylan G-F 20 course(s)			
Study knee	126 (99%)	6 (5%)	
Other knee	53 (42%)	0 (0%)	
Number of patients reporting corticosteroid injection(s)			
Study knee	18 (14%)	89 (70%)	<0.0001
Other knee	8 (6%)	35 (27%)	<0.0001
Number of patients reporting arthroscopy			
Study knee	1 (1%)	5 (4%)	
Other knee	0 (0%)	2 (2%)	
Number of patients reporting total knee replacement (TKR)			
Study knee	1 (1%)	3 (2%)	
Other knee	1 (1%)	1 (1%)	
Number of patients reporting medication for any knee			
Analgesic (oral)	84 (66%)	96 (75%)	0.1158
NSAID (oral)	82 (65%)	101 (79%)	0.0062
Alternative therapy	41 (32%)	44 (34%)	0.5501
Analgesic (topical)	20 (16%)	24 (19%)	0.6996
Other	13 (10%)	25 (20%)	0.0216
Number of patients reporting medications for overall osteoarthritis‡			
Musculoskeletal	16 (13%)	15 (12%)	
CNS	15 (12%)	12 (9%)	
Minerals and vitamins	1 (1%)	1 (1%)	
Anti-infectives	1 (1%)	0 (0%)	
Other	5 (4%)	10 (8%)	

*f is frequency, *n* is sample size.
†*P*-value results from Model 1 adjusting for design variables.
‡If a patient was taking the same medication for knee osteoarthritis and osteoarthritis in other joints, it was included in knee osteoarthritis.
NSAIDs=non-steroidal antiinflammatory drugs; CNS=central nervous system: AC+H=Appropriate Care+ hylan G-F 20; AC=Appropriate Care.

Table III
Primary effectiveness and secondary effectiveness results

	AC+H (*n*=127)	AC (*n*=128)	[(AC+H)−(AC)]	*P*-value*
Primary effectiveness	*n*=127	*n*=127		
Change from baseline to termination in WOMAC pain, mean (S.D.)	−4.4 (3.9)	−1.8 (3.8)	−2.6	0.0001
Change as a % of baseline, mean (S.D.)	−38.4 (34.4)	−13.3 (39.9)	−25.07	<0.0001
Secondary effectiveness f (percent of *n*)†	*n*=127	*n*=127		
Patients improved at termination since baseline:				
WOMAC pain	87 (69%)	51 (40%)	29%	0.0001
WOMAC pain and either stiffness or physical functioning	79 (62%)	45 (35%)	27%	0.0001
Patients global assessment of change since baseline (improved slightly, moderately, or markedly):				
OA in study knee	93 (73%)	35 (27%)	46%	<0.0001
OA in all joints	48 (38%)	22 (17%)	21%	0.0011
Overall health	48 (38%)	21 (16%)	22%	0.0010
Patients global assessment at month 12 over the past 4 weeks (fair, good, or very good):	*n*=124	*n*=107		
OA in study knee	94 (76%)	46 (43%)	33%	<0.0001
OA in all joints	88 (71%)	45 (42%)	29%	<0.0001
Overall health	118 (95%)	91 (85%)	10%	0.0115

**P*-value results from Model 1 adjusting for design variables. The results were similar for model 2 adjusting for design variables and potentially clinically important differences at baseline.
†f is frequency, *n* is sample size. The sample size is indicated in the table heading unless otherwise indicated in the table.
OA=osteoarthritis; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; AC+H=Appropriate Care+hylan G-F 20; AC=Appropriate Care.

health. These data do not address the continuing debate regarding the relative contribution of the intraarticular procedure and the material injected into the knee. However, they clearly demonstrate that making viscosupplementation available as part of an AC treatment regimen results in clinically important improvement to patients with knee OA.

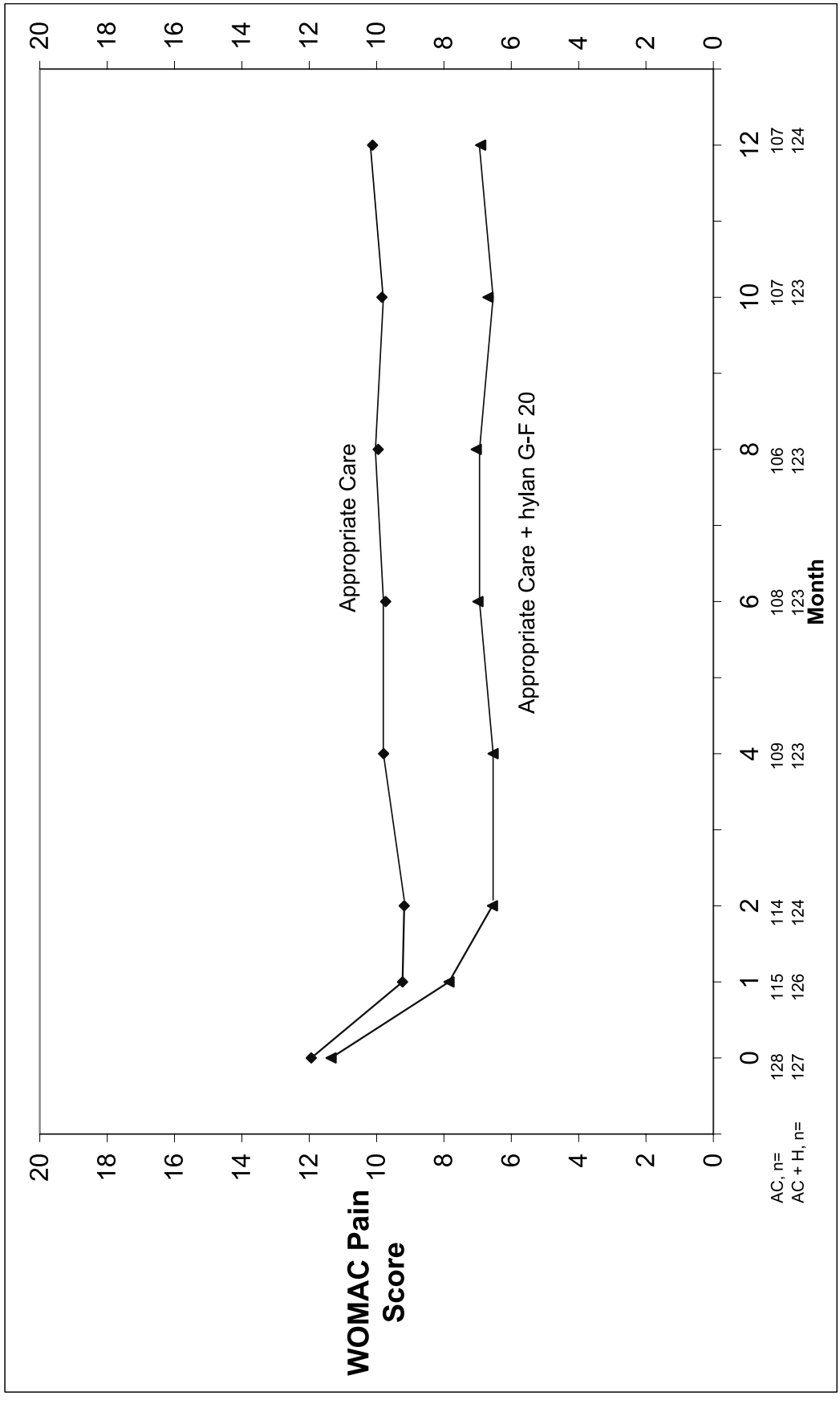

Fig. 2. WOMAC mean pain subscale score by month. WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Table IV
Mean change since baseline in WOMAC, SF-36 and HUI

	Baseline	Month 12	Change (month 12–baseline)*	Change as a % of baseline	*P*-value† for comparison at month 12
WOMAC‡ subscales, mean (S.D.)					
Pain (min: 0; max: 20)					
AC+H	*n*=127	*n*=127			
	11.35 (2.71)	6.94 (3.97)	−4.41 (3.88)	−38.41 (34.39)	<0.0001
AC	*n*=127	*n*=127			
	11.94 (2.89)	10.10 (4.24)	−1.83 (3.83)	−13.34 (39.86)	
(AC+H)−(AC)				−25.07	
Stiffness (min: 0; max: 8)					
AC+H	*n*=127	*n*=124			
	5.06 (1.51)	3.22 (1.74)	−1.83 (1.73)	−34.74 (35.00)	<0.0001
AC	*n*=127	*n*=107			
	5.10 (1.42)	4.31 (1.56)	−0.71 (1.57)	−10.42 (37.42)	
(AC+H)−(AC)				−24.32	
Physical function (min: 0; max: 68)					
AC+H	*n*=127	*n*=124			
	39.54 (9.27)	24.26 (12.95)	−15.04 (12.29)	−37.82 (31.44)	<0.0001
AC	*n*=127	*n*=107			
	40.20 (9.26)	33.87 (13.88)	−5.85 (11.18)	−14.52 (30.39)	
(AC+H)−(AC)				−23.30	
SF-36§, mean (S.D.)					
Aggregate physical component (min: 2; max: 76)					
AC+H	*n*=127	*n*=124			
	28.33 (6.60)	33.24 (10.16)	4.88 (9.78)	20.31 (37.43)	<0.0001
AC	*n*=126	*n*=107			
	28.18 (7.78)	27.78 (8.90)	−0.40 (7.22)	1.07 (29.10)	
(AC+H)−(AC)				19.24	
Aggregate mental component (min: −2; max: 81)					
AC+H	*n*=127	*n*=124			
	51.74 (11.83)	55.29 (10.45)	3.32 (12.06)	11.53 (33.80)	0.0939
AC	*n*=126	*n*=107			
	49.91 (11.82)	52.65 (11.56)	1.55 (10.55)	5.40 (23.11)	
(AC+H)−(AC)				6.13	
HUI3‖ (min: −0.36; max 1), mean (S.D.)					
AC+H	*n*=123	*n*=122			
	0.50 (0.22)	0.63 (0.25)	0.13 (0.23)	n/a	<0.0001
AC	*n*=126	*n*=107			
	0.46 (0.24)	0.51 (0.28)	0.03 (0.22)	n/a	
(AC+H) – (AC)			0.10		

*Due to differences in sample size from baseline to month 12 computation of change (Month 12−Baseline) was calculated for patients with both baseline and termination values.

†*P*-value results from Model 1 adjusting for design variables. The results were similar for model 2 adjusting for design variables and potentially clinically important differences at baseline

‡The higher the score, the worse the problem

§The higher the score, the better the health perception

‖The higher the score, the better the overall health utility

n/a denotes not applicable. Because HUI3 is an interval scale, percent improvements are not useful and indeed distort the magnitude of change.

WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index; AC+H=Appropriate Care+hylan G-F 20; AC=Appropriate Care; SF-36=Short Form 36; HUI3=Health Utilities Index 3.

The data reported that inclusion of hylan G-F 20 in an appropriate care treatment regimen resulted in a meaningful decrease in the utilization of other treatments for knee OA. These decreases were statistically significant with respect to the utilization of steroid injections, oral NSAID therapy and 'other' medications for knee OA. Patients in the AC+H group also received fewer arthroscopies and fewer total knee replacements, but the difference was not compared statistically.

Overall the safety data collected and analysed in this trial confirm that patients treated in different ways are likely to experience different patterns of side effects. Patients in the AC+H group experienced some discomfort associated with the intraarticular procedure. The 15 local adverse events categorized as remotely, possibly or probably attributed to hylan G-F 20 out of a total of approximately 700 hylan G-F 20 injections represents a rate of approximately 2%, similar to that observed in other trials[24]. However, the hylan G-F 20 treated patients also had a clinically meaningful decrease in both the number and severity of GI side effects related to appropriate care and the need for medication to treat GI side effects. Furthermore based on the patients'

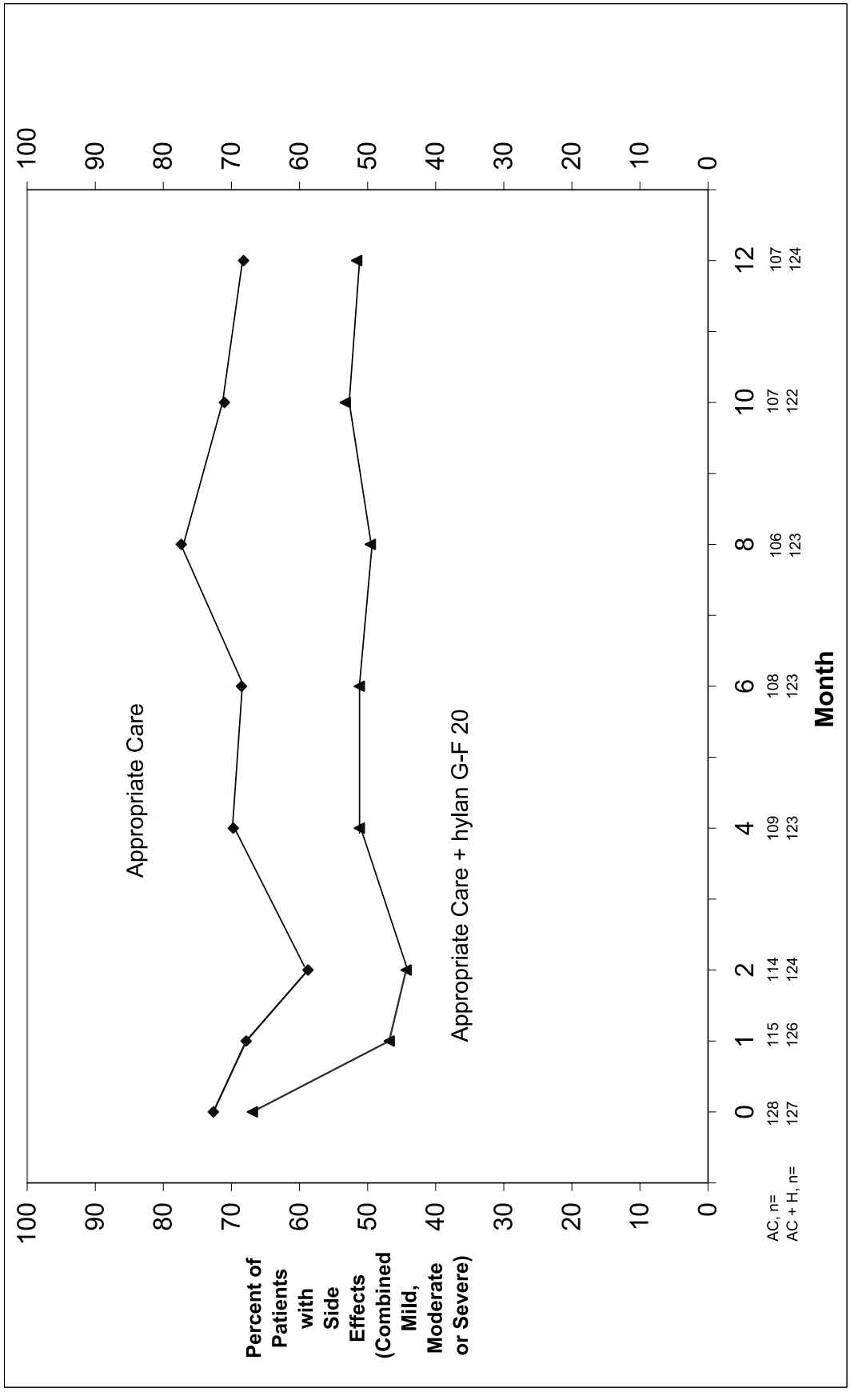

Fig. 3. Percent of patients with global assessment of side effects (combined mild, moderate, or severe) by month.

global evaluation of side effects, it would appear that the patients in the AC+H group judged themselves to have experienced additional benefits by virtue of having encountered fewer side effects. These data suggest that a management strategy, which includes hylan G-F 20 may result in important safety gains, principally by reducing GI events and the necessity for their treatment with GI medications. It should be noted that COX-2 selective inhibitors were not available during the trial.

Although viscosupplementation with hylan G-F 20 is a local treatment which was only used to treat knee OA in this trial, the AC+H group experienced significantly better improvements in global evaluations measuring overall OA, and overall health, and in HRQOL instruments which reflect the health status of the whole patient. This is particularly surprising considering that in the AC+H group 68% of patients had OA in some joint other than the knee and 49% of patients scored their OA in all joints as poor or very poor at baseline (Table I). These 'whole patient' improvements probably reflect the fact that for the patients in this trial the knee was their most symptomatic musculoskeletal problem, and was therefore a major determinant of their pain, disability and HRQOL. It is not uncommon in OA patients for one or two joints to be the primary source of the patient's disability[25]. Similar improvements in HRQOL are observed after surgical treatments for knee OA such as knee replacement[26].

In keeping with the study's pragmatic design, the X-ray grade used to determine study inclusion was that scored by the investigator entering the patient, and based on their best clinical judgement and the radiologist report. The investigator was not asked to provide a grade, but to determine that the patient had OA that was not Grade IV. Hence one radiologist will possibly provide a different rating than the impression of 14 investigators who were not asked to provide a grade. Because the authors were sensitive to potential differences between investigators and to the prevalence of 'borderline' scores, central grading was performed by a trained radiologist. This was done after the patients were entered and used only in the analyses. Patients judged to have Grade IV X-ray by central scoring were not asked to leave the trial.

Grade IV OA of the study knee was an exclusion criterion, because those patients would be more likely to receive surgery, and the intention was to avoid having surgery dominate the cost results. Despite this exclusion criterion, approximately 20–30% of patients in the study were judged by a central radiologist to have grade IV OA. It is not surprising that the grading provided by the site investigators and central radiologist differed for some patients, as the difference between grade level III and IV is subtle. The effectiveness of hylan G-F 20 is not expected to differ significantly for the two grade levels[27]. Patients with grade IV OA are also indicative of real world practice. To address the imbalance in X-ray grades between the two treatment groups, the analyses adjusted for Grade IV OA as a covariate; however, this did not change any results.

The demographics of aging populations make OA a particularly challenging medical and socioeconomic problem[28]. There is therefore a growing pool of patients with symptomatic knee OA who must be managed for many years, and in whom it is desirable to delay knee replacement for as long as possible. Currently the only treatments widely available for such patients are prescription NSAIDS or analgesics, intraarticular steroid injections, topical agents, and arthroscopic lavage and debridement. All of these available modalities have drawbacks or significant side effects. The data presented here indicate that the provision to patients with knee OA of viscosupplementation with hylan G-F 20 within an appropriate care treatment regimen provides benefits in the knee, overall health and health related quality of life at reduced levels of co-therapy and systemic adverse reactions.

Acknowledgments

The authors would like to thank individuals at Biomatrix, Inc. and Innovus Research Inc. who were involved in the study at various stages: Biomatrix, Inc.: Jean Bonomo, Katie Kubler, and Sarita Wilson. Innovus Research Inc.: Bill Bell, Lisa Bernard, Harminder Bilen, Linda Bursic, Helen Crabbe, Paule Desjardins, Julie Gordon, Susan Gow, Lorraine Hotchkies, Marg Hux, Natalie Milkovich, Nancy Ryan, Tammy Sarre, Tammy Slote, Sandra Therrien, John Walker, Irene Zivko, Barb Zrinscak. A special thanks to Shelley Lee for study coordination and Dan Pericak for statistical analysis.

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