The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 23, 2006 VOL. 354 NO. 8

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Daniel O. Clegg, M.D., Domenic J. Reda, Ph.D., Crystal L. Harris, Pharm.D., Marguerite A. Klein, M.S., James R. O'Dell, M.D., Michele M. Hooper, M.D., John D. Bradley, M.D., Clifton O. Bingham III, M.D., Michael H. Weisman, M.D., Christopher G. Jackson, M.D., Nancy E. Lane, M.D., John J. Cush, M.D., Larry W. Moreland, M.D., H. Ralph Schumacher, Jr., M.D., Chester V. Oddis, M.D., Frederick Wolfe, M.D., Jerry A. Molitor, M.D., David E. Yocum, M.D., Thomas J. Schnitzer, M.D., Daniel E. Furst, M.D., Allen D. Sawitzke, M.D., Helen Shi, M.S., Kenneth D. Brandt, M.D., Roland W. Moskowitz, M.D., and H. James Williams, M.D.

ABSTRACT

BACKGROUND

Glucosamine and chondroitin sulfate are used to treat osteoarthritis. The multicenter, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) evaluated their efficacy and safety as a treatment for knee pain from osteoarthritis.

METHODS

We randomly assigned 1583 patients with symptomatic knee osteoarthritis to receive 1500 mg of glucosamine daily, 1200 mg of chondroitin sulfate daily, both glucosamine and chondroitin sulfate, 200 mg of celecoxib daily, or placebo for 24 weeks. Up to 4000 mg of acetaminophen daily was allowed as rescue analgesia. Assignment was stratified according to the severity of knee pain (mild [N=1229] vs. moderate to severe [N=354]). The primary outcome measure was a 20 percent decrease in knee pain from baseline to week 24.

RESULTS

The mean age of the patients was 59 years, and 64 percent were women. Overall, glucosamine and chondroitin sulfate were not significantly better than placebo in reducing knee pain by 20 percent. As compared with the rate of response to placebo (60.1 percent), the rate of response to glucosamine was 3.9 percentage points higher (P=0.30), the rate of response to chondroitin sulfate was 5.3 percentage points higher (P=0.17), and the rate of response to combined treatment was 6.5 percentage points higher (P=0.09). The rate of response in the celecoxib control group was 10.0 percentage points higher than that in the placebo control group (P=0.008). For patients with moderate-to-severe pain at baseline, the rate of response was significantly higher with combined therapy than with placebo (79.2 percent vs. 54.3 percent, P=0.002). Adverse events were mild, infrequent, and evenly distributed among the groups.

CONCLUSIONS

Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain. (ClinicalTrials.gov number, NCT00032890.)

From the University of Utah School of Medicine, Salt Lake City (D.O.C., C.G.J., A.D.S., H.J.W.); the Hines Veterans Affairs Cooperative Studies Program Coordinating Center, Hines, Ill. (D.J.R., H.S.); the Clinical Research Pharmacy Coordinating Center, Albuquerque, N.M. (C.L.H.); the National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Md. (M.A.K.); the University of Nebraska Medical Center, Omaha (J.R.O.); Case Western Reserve University, Cleveland (M.M.H., R.W.M.); the Indiana University School of Medicine, Indianapolis (J.D.B., K.D.B.); the Hospital for Joint Diseases, Rheumatology and Medicine, New York (C.O.B.); Cedars-Sinai Medical Center, Los Angeles (M.H.W.); the University of California, San Francisco (N.E.L.); the Presbyterian Hospital of Dallas, Dallas (J.J.C.); the University of Alabama, Birmingham (L.W.M.); the Hospital of the University of Pennsylvania, Philadelphia (H.R.S.); the University of Pittsburgh (C.V.O.); the Arthritis Research and Clinical Centers, Wichita, Kans. (F.W.); the Virginia Mason Medical Center, Seattle (J.A.M.); the University of Arizona, College of Medicine, Tucson (D.E.Y.); Northwestern University, Chicago (T.J.S.); and the University of California, Los Angeles (D.E.F.). Address reprint requests to Dr. Clegg at the University of Utah, Division of Rheumatology, 4B200 School of Medicine, 50 N. Medical Dr., Salt Lake City, UT 84132, or at gait.study@hsc.utah.edu.

N Engl J Med 2006;354:795-808.

Osteoarthritis is the most common of the arthritides, affecting at least 20 million Americans, a number that is expected to double over the next two decades.[1,2] Currently available medical therapies primarily address the treatment of joint pain in patients with osteoarthritis.[3] Analgesics as well as traditional and cyclooxygenase-2–selective nonsteroidal antiinflammatory drugs (NSAIDs) have suboptimal effectiveness,[4,5] and there is some question about their safety, especially in the light of recent reports of increased cardiovascular risk.[6-8]

The dietary supplements glucosamine and chondroitin sulfate have been advocated, especially in the lay media, as safe and effective options for the management of symptoms of osteoarthritis. A meta-analysis of studies evaluating the efficacy of these supplements for osteoarthritis[9] suggested potential benefit from these agents but raised questions about the scientific quality of the studies. We conducted the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a 24-week, randomized, double-blind, placebo- and celecoxib-controlled, multicenter trial sponsored by the National Institutes of Health, to evaluate rigorously the efficacy and safety of glucosamine, chondroitin sulfate, and the two in combination in the treatment of pain due to osteoarthritis of the knee.

Methods

Patients

Eligible patients were at least 40 years of age and had clinical evidence (knee pain for at least six months and on the majority of days during the preceding month) and radiographic evidence (tibiofemoral osteophytes of at least 1 mm [Kellgren and Lawrence grade 2 or 3]) of osteoarthritis.[10] Patients had to have a summed pain score of 125 to 400 on the index (more symptomatic) knee according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[11,12] and to be in American Rheumatism Association functional class I, II, or III.[13] Patients were excluded if they had concurrent medical or arthritic conditions that could confound evaluation of the index joint, predominant patellofemoral disease, a history of clinically significant trauma or surgery to the index knee, or coexisting disease that could preclude successful completion of the trial. The institutional review board of each participating center approved the study, and all patients gave written informed consent. Patients' race or ethnic group was self-reported.

Treatment Regimens

Eligible patients were randomly assigned with the use of a double-dummy scheme to one of five orally administered treatments: 500 mg of glucosamine hydrochloride three times daily, 400 mg of sodium chondroitin sulfate three times daily, 500 mg of glucosamine plus 400 mg of chondroitin sulfate three times daily, 200 mg of celecoxib (Celebrex, Pfizer) daily, or placebo. Permuted-block randomization was used with random block sizes, stratified according to the 16 clinical centers and baseline WOMAC pain stratum (mild, defined as a score of 125 to 300, or moderate to severe, defined as a score of 301 to 400; scores on this scale can range from 0 to 500). The randomization code list was developed by the Veterans Affairs Cooperative Studies Program Data Coordinating Center in Hines, Illinois. During data collection, neither the clinical centers nor the coordinating center at the University of Utah had access to the randomization codes or statistical summaries of follow-up data. Patients were allowed to take up to 4000 mg of acetaminophen (Tylenol, McNeil) daily, except during the 24 hours before a clinical evaluation for joint pain. Other analgesics, including narcotics and NSAIDs, were not permitted. Patients were evaluated at baseline and 4, 8, 16, and 24 weeks after randomization.

Outcome Measures

The primary outcome measure was a response to treatment, defined a priori by expert consensus as a 20 percent decrease in the summed score for the WOMAC pain subscale from baseline to week 24. Secondary outcome measures, selected a priori in accordance with the preliminary recommendations of the Osteoarthritis Research Society International (OARSI) task force,[14] included the following: scores for the stiffness and function subscales of WOMAC; the patient's global assessments of disease status and response to therapy, obtained with the use of a 100-mm visual-analogue scale on which higher scores indicate more severe disease; the investigator's global assessment of disease status, obtained with the use of a 100-mm visual-analogue scale; the presence or

absence of soft-tissue swelling, effusion, or both in the index knee; scores on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which reflect the health-related quality of life[15]; scores on the Health Assessment Questionnaire, which reflect physical function[16]; and acetaminophen use, according to diary entries and tablet counts. All outcome measures were assessed at each study visit, except for the patient's global assessment of response to therapy, which was assessed only after randomization.

In May 2004, the Outcome Measures in Rheumatology Clinical Trials (OMERACT) and OARSI published their criteria for a response to treatment for osteoarthritis.[17] A response was classified as an improvement in pain or function of at least 50 percent and a decrease of at least 20 mm on the visual-analogue scale for pain or function or the occurrence of at least two of the following: a decrease in pain of at least 20 percent and at least 10 mm on the visual-analogue scale; an improvement in function of at least 20 percent and a decrease of at least 10 mm on the visual-analogue scale; and an increase in the patient's global assessment score by at least 20 percent and at least 10 mm on the visual-analogue scale. Since we prospectively collected data on each component, the OMERACT–OARSI response rate is also reported.

PRODUCT SELECTION

Our study was conducted under an investigational new drug application, and the study agents were subject to pharmaceutical regulation by the Food and Drug Administration (FDA). The Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, a facility licensed by the FDA, used a vendor-certification program to evaluate available commercial products and raw materials in order to select the suppliers of glucosamine and chondroitin sulfate. Donated or purchased ingredients were tested for purity, potency, and quality. Certificates of analysis were obtained for the agents, and Drug Master Files were on file with the FDA. Capsules containing 250 mg of glucosamine hydrochloride, 200 mg of sodium chondroitin sulfate, the two in combination, and matching placebo were manufactured, distributed, and placed on a shelf-life–stability program throughout the study at the Pharmacy Coordinating Center. In addition, 200-mg capsules of celecoxib were purchased and overencapsulated (for masking) and a matching placebo was prepared.

ADVERSE EVENTS

Adverse events and serious adverse events were assessed by the investigator at each study visit and followed until resolution. Safety monitoring included complete blood counts; measurement of serum aspartate aminotransferase, alanine aminotransferase, glucose, creatinine, and partial-thromboplastin time; and urinalysis at each study visit. Specific cardiovascular monitoring for adverse events was not done. Patients with abnormal blood glucose results had blood glucose levels measured after an overnight fast. In patients with diabetes at enrollment, fasting blood glucose and glycosylated hemoglobin levels were monitored. A test for fecal occult blood (Hemoccult, Beckman Coulter) was performed at the visit at week 24. Medication was withdrawn from patients in whom diabetes or gastrointestinal bleeding developed, and the patients were referred for further evaluation.

STATISTICAL ANALYSIS

An absolute increase in the response rate of 15 percent, as compared with the rate in the placebo group, was considered to indicate a clinically meaningful treatment effect. We estimated that 1588 patients would need to be enrolled to provide the study with a statistical power of 85 percent to detect one or more clinically meaningful differences between the placebo group and the glucosamine group, the chondroitin sulfate group, and the combined-treatment group, assuming a rate of response of 35 percent in the placebo group and a withdrawal rate of 20 percent. Pairwise comparisons of the glucosamine group, the chondroitin sulfate group, and the combined-treatment group with the placebo group were made with the use of a two-sided chi-square test with an α value of 0.017 for each comparison (overall α value, 0.05). A side comparison between celecoxib and placebo also used an α value of 0.017. The data and safety monitoring board reviewed study performance and safety data annually but did not conduct interim monitoring of the primary outcome. Analysis of the primary outcome measure was conducted according to the intention to treat.

Analyses of the secondary outcome measures followed the pairwise-comparison plan described

above. The chi-square test was used to compare categorical data. The t-test for independent groups was used to compare changes between groups in quantitative data from baseline to the end of follow-up. A total of 71 patients who did not attend any follow-up visits were classified as having no response for the primary outcome measure, the OMERACT–OARSI response, and a response based on a 50 percent reduction in the score for the WOMAC pain subscale. These patients were excluded from the analyses of all other secondary outcomes. We used the last-observation-carried-forward method in the analysis of all outcomes among patients who made at least one follow-up visit but who did not complete follow-up.

We also analyzed the results according to the WOMAC pain stratum, since logistic-regression analysis showed a significant (P=0.008) interaction between treatment and pain stratum in the comparison of combined treatment with placebo for the primary outcome measure. All statistical tests were two-sided. We used SAS software (version 8) for all statistical analyses.[18]

RESULTS

CHARACTERISTICS OF THE PATIENTS

Recruitment began November 29, 2000, at 13 clinical centers, and 3 centers were added to the study in February 2003 to ensure timely recruitment. The study was completed on July 8, 2004. A total of 3238 patients were screened, and 1583 underwent randomization (Fig. 1). The most common reasons for exclusion were an inability to meet radiographic criteria (in 1089 patients) and a WOMAC pain score of less than 125 or more than 400 (in 321 patients). The majority of patients were women (64.1 percent), with a mean age of 58.6 years and a mean body-mass index (the weight in kilograms divided by the square of the height in meters) of 31.7. The groups were well balanced at baseline (Table 1). The withdrawal rate of 20.5

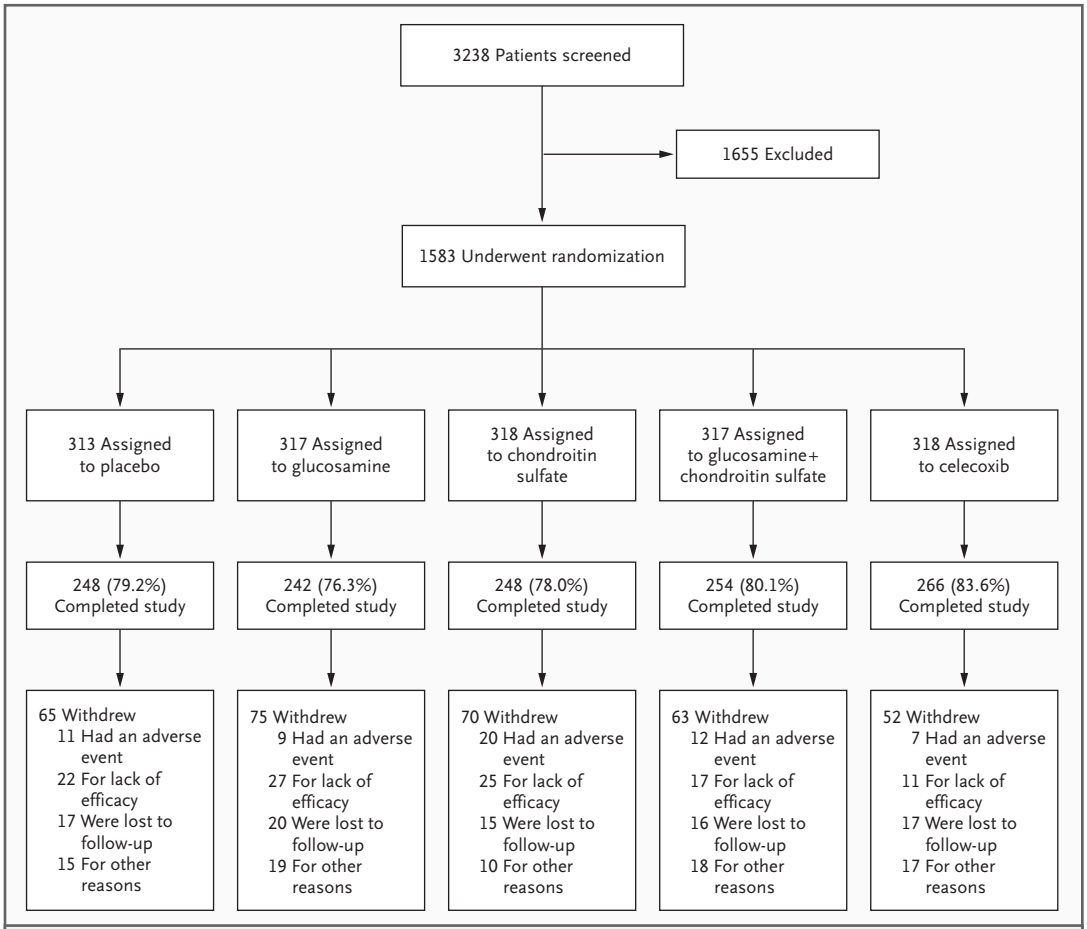

Figure 1. Enrollment and Outcomes.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=313)	Glucosamine (N=317)	Chondroitin Sulfate (N=318)	Glucosamine + Chondroitin Sulfate (N=317)	Celecoxib (N=318)
Age — yr	58.2±9.8	58.6±10.2	58.2±10.0	58.6±10.6	59.4±11.1
Female sex — no. (%)	200 (63.9)	199 (62.8)	205 (64.5)	199 (62.8)	212 (66.7)
Race — no. (%)					
White	247 (78.9)	259 (81.7)	242 (76.1)	235 (74.1)	256 (80.5)
Black	39 (12.5)	42 (13.2)	41 (12.9)	54 (17.0)	45 (14.2)
Other	27 (8.6)	16 (5.0)	35 (11.0)	28 (8.8)	17 (5.3)
Hispanic — no. (%)	18 (5.8)	13 (4.1)	19 (6.0)	17 (5.4)	8 (2.5)
Body-mass index	31.9±7.3	31.8±6.8	32.0±7.6	31.5±6.6	31.5±7.1
Duration of osteoarthritis symptoms — yr	9.5±9.1	10.4±10.5	9.7±10.0	10.1 ±10.2	10.1±9.2
Time since diagnosis of osteoarthritis — yr	5.3.±7.1	6.0±7.9	5.1±7.1	6.1±8.6	5.2±6.4
No. of 500-mg acetaminophen tablets/day	1.2±2.1	1.2±2.0	1.2±1.8	1.1±1.9	1.2±1.9
ARA functional class — no. (%)					
I	80 (25.6)	79 (24.9)	82 (25.8)	80 (25.2)	81 (25.5)
II	169 (54.0)	194 (61.2)	180 (56.6)	182 (57.4)	186 (58.5)
III	64 (20.4)	44 (13.9)	56 (17.6)	55 (17.4)	49 (15.4)
Unknown	0	0	0		2 (1)
Kellgren and Lawrence radiographic reading grade 2 — no. (%)	179 (57.2)	173 (54.6)	186 (58.5)	160 (50.5)	177 (55.7)
Global assessment of disease status score					
Physician	47.7±21.2	47.9±22.1	47.1±20.0	48.1±20.6	48.0±21.6
Patient	51.4±18.2	50.1±18.0	51.5±19.05	51.2±18.3	49.5±19.2
Joint swelling, effusion, or both on clinical examination — no. (%)	88 (28.1)	79 (24.9)	90 (28.3)	86 (27.1)	83 (26.1)
WOMAC score					
Pain subscale	237.1±74.2	233.3±74.8	235.3±71.5	239.1±72.1	234.9±74.3
Stiffness subscale	106.6±42.7	106.2±43.9	106.6±42.8	105.2±42.0	107.4±42.1
Function subscale	765.8±312.2	760.8±328.2	778.9±304.3	768.2±298.2	788.2±309.0
Normalized	145.8±48.4	144.5±49.5	146.0±46.5	145.6±45.9	147.0±47.6
Health Assessment Questionnaire score					
Alternative Disability	0.79±0.42	0.77±0.37	0.76±0.42	0.80±0.37	0.78±0.41
Pain	55.1±20.9	53.8±20.7	52.5±19.8	54.3±19.4	54.9±20.9
SF-36 score					
Physical component	37.0±8.2	37.8±7.9	37.6±7.7	36.5±7.6	37.2±7.7
Mental component	53.5±9.8	53.2±9.8	53.9±9.3	53.4±10.2	53.8±9.3

* Plus–minus values are means ±SD. Race or ethnic group was self-determined. The body-mass index is the weight in kilograms divided by the square of the height in meters. Patient's and physician's global assessment scores can range from 0 to 100. Scores for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) can range from 0 to 500 for the pain subscale, 0 to 200 for the stiffness subscale, and 0 to 1700 for the function subscale; normalized scores can range from 0 to 300. Scores for the Health Assessment Questionnaire can range from 0 to 3 for the Alternative Disability portion and from 0 to 100 for the Pain portion. Scores for the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) can range from 4 to 71 for the physical component and from 2 to 74 for the mental component. For all instruments, higher scores indicate more severe disease. ARA denotes American Rheumatism Association (now called the American College of Rheumatology).

percent did not differ significantly among the groups and was similar to the predicted rate of 20 percent. Adherence to the assigned treatment regimen, measured by capsule count at each visit, ranged from 88.8 percent to 97.0 percent.

CLINICAL OUTCOMES

Figure 2 shows the relative likelihood of a response and 98.3 percent confidence intervals (corresponding to the use of criteria in which a P value of less than 0.017, rather than less than 0.05, indicated statistical significance, owing to multiple comparisons) for the total study population as well as both pain strata for each group, as compared with the placebo group. Results of primary and secondary outcome measures for the entire study population and each WOMAC pain stratum are given in Table 2.

Overall, differences between placebo and the various agents were relatively small. Analysis of the primary outcome measure revealed that the rate of response to glucosamine and chondroitin sulfate, either alone or in combination, was not significantly higher than the rate of response to placebo. As compared with the rate of response to placebo, the rate of response to chondroitin sulfate was 5.3 percentage points higher (P=0.17), the rate of response to glucosamine was 3.9 percentage points higher (P=0.30), and the rate of response to the combination of glucosamine and chondroitin sulfate was 6.5 percentage points higher (P=0.09). The rate of response to the celecoxib control was 10.0 percentage points higher than that for the placebo control (P=0.008). The OMERACT–OARSI response rates showed a similar pattern, with differences between the placebo group and the glucosamine, chondroitin sulfate, and combined-treatment groups not reaching significance. As compared with the rate of response to placebo, the rate of response to chondroitin

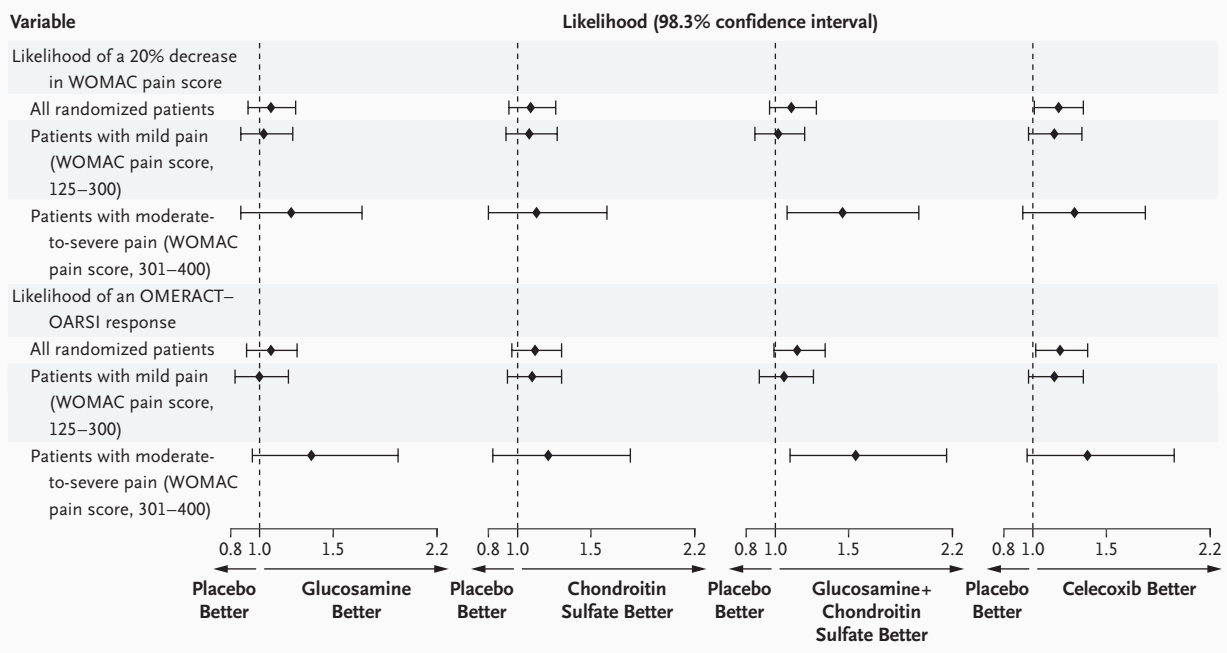

Figure 2. Pairwise Comparisons of the Overall Likelihood of a Response.

Scores for the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) can range from 0 to 500, with higher scores indicating more pain. A response according to the guidelines of the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT–OARSI) was classified as an improvement in function or pain of at least 50 percent and a decrease of at least 20 mm on the visual-analogue scale for pain or function or the occurrence of at least two of the following: a decrease in pain of at least 20 percent and at least 10 mm on the visual-analogue scale; an improvement in function of at least 20 percent and a decrease of at least 10 mm on the visual-analogue scale; and an increase in the patient's global assessment score by at least 20 percent and at least 10 mm on the visual-analogue scale.

Table 2. Primary and Secondary Outcomes.*

Outcome	Placebo	Glucosamine	Chondroitin Sulfate	Glucosamine + Chondroitin Sulfate	Celecoxib
All randomized patients					
No. of patients	313	317	318	317	318
Primary outcome: 20% decrease in WOMAC pain score					
At end of follow-up — no. (%)	188 (60.1)	203 (64.0)	208 (65.4)	211 (66.6)	223 (70.1)
P value		0.30	0.17	0.09	0.008†
Secondary outcomes					
OMERACT–OARSI response					
At end of follow-up — no. (%)	178 (56.9)	192 (60.6)	202 (63.5)	208 (65.6)	214 (67.3)
P value		0.35	0.09	0.02‡	0.007†
50% decrease in WOMAC pain score					
At end of follow-up — no. (%)	132 (42.2)	147 (46.4)	134 (42.1)	147 (46.4)	159 (50.0)
P value		0.29	0.99	0.29	0.05‡
WOMAC pain score					
Change from baseline	−86.1±114.2	−82.9±115.4	−83.9±106.3	−100.5±112.7	−100.0±102.9
At end of follow-up	151.0±113.1	149.3±115.9	151.7±113.1	137.9±102.3	135.7±108.3
P value		0.73	0.81	0.12	0.12
WOMAC stiffness score					
Change from baseline	−36.4±52.3	−34.7±52.5	−31.2±51.5	−39.2±52.6	−41.5±50.3
At end of follow-up	70.5±48.8	70.6±52.2	75.6±51.7	66.2±47.8	66.7±51.4
P value		0.68	0.22	0.53	0.23
WOMAC function score					
Change from baseline	−227.4±362.7	−222.3±388.3	−235.6±346.6	−276.5±358.0	−289.3±340.7
At end of follow-up	540.3±374.1	531.8±388.6	544.1±394.1	490.8±348.9	500.1±382.7
P value		0.87	0.78	0.10	0.03
Normalized WOMAC score					
Change from baseline	−48.8±65.1	−47.1±66.9	−46.2±62.2	−56.0±63.7	−57.7±59.8
At end of follow-up	97.2±66.1	96.4±69.1	100.0±68.3	89.5±61.6	89.9±66.8
P value		0.75	0.61	0.18	0.08
HAQ Alternative Disability score					
Change from baseline	−0.16±0.36	−0.18±0.36	−0.17±0.34	−0.20±0.39	−0.20±0.35
At end of follow-up	0.63±0.44	0.59±0.44	0.59±0.45	0.59±0.41	0.58±0.45
P value		0.59	0.93	0.25	0.18
HAQ Pain score					
Change from baseline	−16.6±28.0	−16.0±29.1	−15.4±25.5	−20.8±28.8	−20.2±27.4
At end of follow-up	38.4±25.2	37.5±26.9	37.3±26.1	33.7±25.0	34.9±25.8
P value		0.82	0.60	0.07	0.11
Patient's global assessment of response to therapy score					
At end of follow-up — no. (%)	45.2±30.5	45.3±31.8	45.6±30.9	43.1±30.4	41.7±31.0
P value		0.96	0.89	0.39	0.16

Table 2. (Continued.)

Outcome	Placebo	Glucosamine	Chondroitin Sulfate	Glucosamine + Chondroitin Sulfate	Celecoxib
Patient's global assessment of disease status score					
Change from baseline	−13.6±27.5	−12.3±27.4	−12.4±24.5	−15.7±28.2	−14.9±27.1
At end of follow-up	34.0±23.9	35.1±25.7	34.8±24.7	32.4±23.3	33.2±25.1
P value		0.56	0.58	0.36	0.55
Physician's global assessment of disease status score					
Change from baseline	−14.6±23.4	−12.1±26.3	−13.7±23.2	−15.6±25.3	−13.2±23.0
At end of follow-up	37.1±22.5	37.9±23.3	37.6±22.7	35.7±21.9	36.2±21.9
P value		0.23	0.64	0.60	0.49
Joint swelling, effusion, or both on clinical examination					
At baseline — no. (%)	88 (28.1)	79 (24.9)	90 (28.3)	86 (27.1)	83 (26.1)
At end of follow-up — no./total no. (%)	58/292 (19.9)	56/304 (18.4)	38/307 (12.4)	62/300 (20.7)	41/306 (13.4)
P value		0.65	0.01†	0.81	0.03‡
No. of 500-mg tablets of acetaminophen					
At baseline — no. (%)	1.2±2.1	1.2±2.0	1.2±1.8	1.1±1.9	1.2±1.9
At end of follow-up — no. (%)	1.8±1.8	1.7±1.7	1.9±1.9	1.7±1.8	1.6±1.7
P value		0.53	0.61	0.29	0.09
Patients with moderate-to-severe pain (WOMAC pain score, 301–400)					
No. of patients	70	70	70	72	72
Primary outcome: 20% decrease in WOMAC pain score					
At end of follow-up — no. (%)	38 (54.3)	46 (65.7)	43 (61.4)	57 (79.2)	50 (69.4)
P value		0.17	0.39	0.002†	0.06
Secondary outcomes					
OMERACT–OARSI response					
At end of follow-up — no. (%)	34 (48.6)	46 (65.7)	41 (58.6)	54 (75.0)	48 (66.7)
P value		0.04	0.24	0.001†	0.03‡
50% decrease in WOMAC pain score					
At end of follow-up — no. (%)	23 (32.9)	29 (41.4)	25 (35.7)	38 (52.8)	33 (45.8)
P value		0.29	0.72	0.02‡	0.11
WOMAC pain score					
Change from baseline	−123.0±134.8	−141.0±129.4	−120.7±128.5	−177.5±97.8	−153.2±125.3
At end of follow-up	218.6±132.9	199.9±125.1	216.8±126.7	164.5±100.0	188.4±124.0
P value		0.44	0.92	0.009†	0.18
WOMAC stiffness score					
Change from baseline	−41.1±59.0	−53.9±56.5	−30.2±56.7	−56.7±50.4	−54.2±50.1
At end of follow-up	102.5±52.9	89.4±55.2	100.0±56.6	80.6±49.8	81.8±56.3
P value		0.21	0.28	0.11	0.17
WOMAC function score					
Change from baseline	−291.6±428.1	−405.8±416.7	−284.7±389.0	−473.8±332.7	−410.8±402.3
At end of follow-up	769.1±434.9	699.2±410.5	773.8±459.5	614.2±352.5	657.5±435.6
P value		0.13	0.92	0.008†	0.10

Table 2. (Continued.)

Outcome	Placebo	Glucosamine	Chondroitin Sulfate	Glucosamine + Chondroitin Sulfate	Celecoxib
Normalized WOMAC score					
Change from baseline	−62.3±77.3	−79.0±73.8	−55.2±73.5	−91.7±59.6	−81.9±68.3
At end of follow-up	140.2±75.8	125.8±74.1	138.9±76.9	109.3±62.3	117.2±75.9
P value		0.21	0.58	0.017†	0.12
HAQ Alternative Disability score					
Change from baseline	−0.19±0.38	−0.27±0.37	−0.19±0.40	−0.27±0.41	−0.29±0.35
At end of follow-up	0.81±0.50	0.69±0.37	0.80±0.54	0.70±0.49	0.70±0.44
P value		0.24	0.95	0.28	0.12
HAQ Pain score					
Change from baseline	−22.1±31.5	−27.1±28.6	−16.9±27.3	−33.1±26.4	−30.7±26.8
At end of follow-up	48.7±27.2	43.9±25.7	50.3±27.2	37.3±24.7	40.4±28.3
P value		0.35	0.31	0.03‡	0.09
Patient's global assessment of response to therapy score					
At end of follow-up	48.1±29.8	42.9±29.0	53.5±28.6	38.0±24.2	39.9±29.9
P value		0.32	0.29	0.04	0.11
Patient's global assessment of disease status score					
Change from baseline	−18.6±32.1	−22.2±27.0	−14.2±26.8	−28.3±25.2	−24.4±28.2
At end of follow-up	41.9±26.2	40.9±26.5	44.2±27.0	35.2±21.6	38.6±26.8
P value		0.49	0.40	0.05	0.26
Physician's global assessment of disease status score					
Change from baseline	−17.8±24.3	−15.4±27.7	−18.3±22.5	−17.6±23.7	−19.4±23.3
At end of follow-up	42.5±23.4	40.4±22.6	42.3±22.7	36.8±20.0	36.3±21.2
P value		0.61	0.90	0.97	0.70
Joint swelling, effusion, or both on clinical examination					
At baseline — no. (%)	25 (35.7)	21 (30.0)	21 (30.0)	21 (29.2)	25 (34.7)
At end of follow-up — no./total no. (%)	14/64 (21.9)	15/65 (23.1)	10/67 (14.9)	15/66 (22.7)	7/69 (10.1)
P value		0.87	0.30	0.91	0.06
No. of 500-mg acetaminophen tablets/day					
At baseline	2.2±2.6	2.3±2.2	2.3±2.2	1.9±3.1	1.9±2.0
At end of follow-up	2.3±1.7	2.5±2.2	2.5±2.1	1.9±1.9	2.1±1.8
P value		0.56	0.67	0.17	0.42
Patients with mild pain (WOMAC pain score, 125–300)					
No. of patients	243	247	248	245	246
Primary outcome: 20% decrease in WOMAC pain score					
At end of follow-up — no. (%)	150 (61.7)	157 (63.6)	165 (66.5)	154 (62.9)	173 (70.3)
P value		0.67	0.27	0.80	0.04‡
Secondary outcomes					
OMERACT–OARSI response					
At end of follow-up — no. (%)	144 (59.3)	146 (59.1)	161 (64.9)	154 (62.9)	166 (67.5)
P value		0.97	0.20	0.42	0.06

Table 2. (Continued.)

Outcome	Placebo	Glucosamine	Chondroitin Sulfate	Glucosamine + Chondroitin Sulfate	Celecoxib
50% decrease in WOMAC pain score					
At end of follow-up — no. (%)	109 (44.9)	118 (47.8)	109 (44.0)	109 (44.5)	126 (51.2)
P value		0.52	0.84	0.94	0.16
WOMAC pain score					
Change from baseline	−75.6±105.6	−67.1±106.2	−73.5±97.0	−78.8±107.1	−84.5±89.9
At end of follow-up	131.8±99.0	135.5±109.6	133.2±101.9	130.4±101.9	120.4±98.4
P value		0.39	0.83	0.74	0.33
WOMAC stiffness score					
Change from baseline	−35.1±50.3	−29.5±50.2	−31.5±50.0	−34.2±52.2	−37.8±49.8
At end of follow-up	61.4±43.6	65.5±50.2	68.7±48.1	62.1±46.5	62.3±49.1
P value		0.22	0.44	0.85	0.57
WOMAC function score					
Change from baseline	−209.2±340.7	−172.4±365.5	−221.8±333.2	−220.9±345.6	−253.9±312.7
At end of follow-up	475.3±328.0	486.3±370.4	479.3±348.1	456.0±340.7	454.2±353.9
P value		0.26	0.68	0.71	0.14
Normalized WOMAC score					
Change from baseline	−45.0±60.9	−38.4±62.3	−43.6±58.5	−45.9±61.3	−50.7±55.3
At end of follow-up	85.0±57.9	88.4±65.6	89.0±61.5	84.0±60.3	81.9±61.9
P value		0.25	0.81	0.87	0.29
HAQ Alternative Disability score					
Change from baseline	−0.16±0.36	−0.16±0.35	−0.16±0.33	−0.18±0.38	−0.18±0.35
At end of follow-up	0.58±0.41	0.56±0.41	0.54±0.40	0.56±0.39	0.54±0.44
P value		0.99	0.89	0.39	0.37
HAQ Pain score					
Change from baseline	−15.0±26.8	−13.1±28.6	−15.0±25.0	−17.2±28.6	−17.2±26.8
At end of follow-up	35.4±23.9	35.8±27.0	33.7±24.7	32.7±25.0	33.3±24.9
P value		0.46	1.00	0.39	0.37

sulfate was 6.6 percentage points higher (P=0.09), the rate of response to glucosamine was 3.7 percentage points higher (P=0.35), and the rate of response to combined treatment was 8.7 percentage points higher (P=0.02). With the exception of the incidence of joint swelling, effusion, or both, for the secondary outcome measures, there were no significant differences between the placebo group and the glucosamine, chondroitin sulfate, or combined-treatment groups.

Analysis of the primary outcome in the subgroup of patients with mild pain showed even smaller treatment effects, with the rate of response ranging from 8.6 percentage points higher in the celecoxib group to 1.9 percentage points higher in the glucosamine group than in the placebo group. None of the differences were significant. Treatment effects in the moderate-to-severe pain stratum were more substantial. Results for the primary outcome in this stratum, which included 22 percent of the patients in the trial, indicated that combined treatment was significantly more effective than placebo (24.9 percentage points higher, P=0.002). As compared with placebo, however, celecoxib (difference, 15.1 percentage points; P=0.06), glucosamine (difference, 11.4 percentage points; P=0.17), and chondroitin sulfate (difference, 7.1 percentage points; P=0.39) were not significantly better. Similarly, the OMERACT–OARSI response rate ranged from 26.4 percentage points higher with combined treatment (P=0.001) to 10.0 percentage points higher with

Table 2. (Continued.)

Outcome	Placebo	Glucosamine	Chondroitin Sulfate	Glucosamine + Chondroitin Sulfate	Celecoxib
Patient's global assessment of response to therapy score					
At end of follow-up	44.4±30.7	46.0±32.5	43.3±31.2	44.5±31.9	42.2±31.3
P value		0.59	0.70	0.97	0.45
Patient's global assessment of disease status score					
Change from baseline	−12.2±26.0	−9.6±26.9	−11.9±23.8	−12.1±28.0	−12.2±26.2
At end of follow-up	31.8±22.8	33.5±25.3	32.2±23.3	31.6±23.8	31.7±24.4
P value		0.30	0.90	0.98	1.00
Physician's global assessment of disease status score					
Change from baseline	−13.7±23.1	−11.2±25.9	−12.4±23.3	−15.0±25.7	−11.4±22.7
At end of follow-up	35.6±22.1	37.2±23.4	36.3±22.6	35.4±22.4	36.2±22.1
P value		0.29	0.55	0.54	0.30
Joint swelling, effusion, or both on clinical examination					
At baseline — no. (%)	63 (26.0)	58 (23.5)	69 (27.8)	65 (26.5)	58 (23.6)
At end of follow-up — no./total no. (%)	44/228 (19.3)	41/239 (17.2)	28/240 (11.7)	47/234 (20.1)	34/237 (14.3)
P value		0.55	0.02‡	0.83	0.15
No. of 500-mg acetaminophen tablets/day					
At baseline	1.5±2.1	1.4±2.0	1.2±1.8	1.3±1.7	1.4±2.0
At end of follow-up	1.7±1.7	1.5±1.5	1.7±1.8	1.6±1.7	1.4±1.6
P value		0.28	0.73	0.65	0.12

* Plus–minus values are means ±SD. All P values are for the comparison with the placebo group. WOMAC denotes Western Ontario and McMaster Universities Osteoarthritis Index, OMERACT–OARSI Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society, and HAQ Health Assessment Questionnaire.
† P≤0.017 for the comparison with placebo.
‡ P≤0.05 for the comparison with placebo.

chondroitin sulfate (P=0.24), as compared with placebo.

Overall, the rate of use of rescue acetaminophen was low (1.6 to 1.9 tablets per day) (Table 2). There were no significant differences in the use of acetaminophen among the groups for all randomized patients or within each pain stratum.

ADVERSE EVENTS

Seventy-seven serious adverse events were reported in 61 patients. Three serious adverse events were judged by the investigator to be related to study treatment: congestive heart failure (in a patient receiving combined treatment), stroke (in a patient receiving celecoxib), and chest pain (in a patient receiving glucosamine). There were no serious gastrointestinal adverse events or deaths. The number of patients who withdrew because of adverse events was similar among the groups (Fig. 1).

Adverse events were generally mild and evenly distributed among the groups. As compared with the placebo group, the celecoxib group had a significantly lower incidence of headache and nausea but had a nonsignificant but higher incidence of increased blood pressure. Patients who received chondroitin sulfate had the highest incidence of "musculoskeletal and connective-tissue" events and the lowest incidence of vomiting. Because of concern about the possibility of ischemic cardiovascular events with the use of selective cyclooxygenase-2 inhibitors, the data and safety monitoring board requested an interim review of adverse events. Although the celecoxib group had a nonsignificant but higher incidence of "cardiac" events than the other four groups, these events were predominantly arrhythmias (palpitations and atrial fibrillation), rather than ischemic events.

TIME TO RESPONSE

Figure 3 shows the percentage of patients with a primary response in each group at weeks 4 and 24.

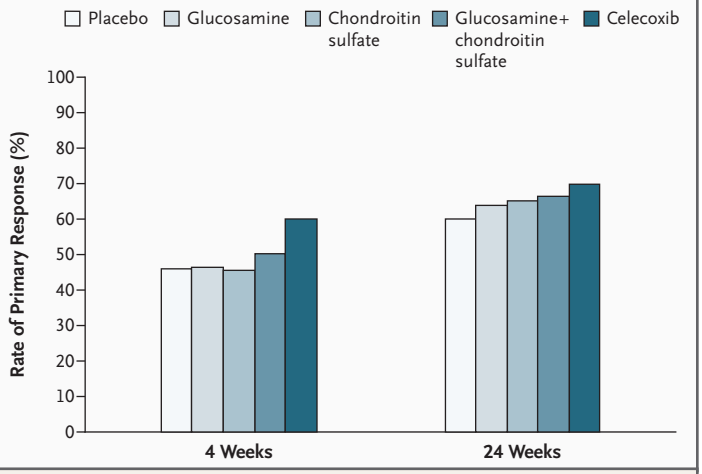

Figure 3. Rates of a Primary Response in the Five Groups at 4 and 24 Weeks.

A primary response was defined as a 20 percent decrease in the summed score for the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index.

The onset of pain relief was fastest in the celecoxib group, with substantial improvement at four weeks. The other four groups had more gradual improvement.

DISCUSSION

Osteoarthritis is the most common form of arthritis in the United States and has a major effect on the health-related quality of life. In 2004, the estimated direct and indirect medical costs associated with all forms of arthritis exceeded $86 billion.[2] Glucosamine and chondroitin sulfate are the most widely used dietary supplements for osteoarthritis, with estimated sales in 2004 approaching $730 million.[19] GAIT was designed to evaluate rigorously the efficacy of glucosamine, chondroitin sulfate, and the two in combination in treating knee pain related to osteoarthritis. The analysis of the primary outcome measure did not show that either supplement, alone or in combination, was efficacious. Analysis of the prespecified subgroup of patients with moderate-to-severe pain demonstrated that combination therapy significantly decreased knee pain related to osteoarthritis, as measured by the primary outcome or by the OMERACT–OARSI response rate. We did not identify significant benefits associated with the use of glucosamine or chondroitin sulfate alone. Although the results for glucosamine did not reach significance, the possibility of a positive effect in the subgroup of patients with moderate-to-severe pain cannot be excluded, since the difference from placebo in the OMERACT–OARSI response rate approached significance in this group. Treatment with chondroitin sulfate was associated with a significant decrease in the incidence of joint swelling, effusion, or both. We did not find an increased risk of ischemic cardiovascular events among patients who received celecoxib or among patients with diabetes who received glucosamine, but this study was not powered to assess these risks.

Our study has a number of limitations. First, the high rate of response to placebo (60.1 percent) and the relatively mild degree of pain from osteoarthritis among the participants may have limited our ability to detect benefits of the treatments. Elevated rates of response to placebo have been reported in other osteoarthritis trials[20,21] and may relate, in part, to patients' biases and expectations and to the enrollment of patients with relatively mild symptoms of osteoarthritis. In addition, our patients had relatively mild knee pain at baseline, as compared with that in classic studies of osteoarthritis, in which a criterion for entry was a disease flare after the discontinuation of NSAIDs.[22,23] Widely used outcome measures for osteoarthritis treatments may be insensitive in identifying improvement, making it difficult to identify improvement in patients with mild symptoms. The OMERACT–OARSI response outcome seemed to perform best in the face of these challenges (as it was designed to do). Thus, it is not clear whether the small but consistently positive differences between groups in some of the analyses represent clinically meaningful effects obscured by the factors outlined above or effects of marginal clinical value. However, even the effects of celecoxib were smaller than those seen in other studies.[24]

Treatment effects were more substantial in the subgroup of patients with moderate-to-severe pain, but the relatively small numbers of patients in this subgroup may have limited the study's power to demonstrate significant benefits in the glucosamine, chondroitin sulfate, and celecoxib groups. For example, as compared with placebo, celecoxib therapy was associated with a clinically meaningful difference in the primary outcome measure of 15 percentage points, but the difference did not reach statistical significance.

Several studies have evaluated the efficacy of glucosamine[25-29] and chondroitin sulfate.[30,31] Some

have demonstrated efficacy but have been criticized as having flaws, which were addressed in the design of GAIT, such as the failure to adhere to the intention-to-treat principle, the enrollment of small numbers of patients, potential bias related to sponsorship of the study by the manufacturers of the dietary supplements, and inadequate masking of the study agent. In general, these studies have recruited patients with lower levels of knee pain[26-29] and failed to show improvement in WOMAC pain scores.[32] However, in some instances,[26,27] benefits of glucosamine have been demonstrated with the use of other outcome measures.

In the United States, glucosamine and chondroitin sulfate are considered dietary supplements and are not held to the stringent standards of pharmaceutical manufacture. If these agents are to be widely used for the treatment of osteoarthritis, serious consideration must be given to their current regulatory status in order to ensure potency and purity. Studies have demonstrated substantial variation between the content listed on the labels of these products and the actual content.[33-35] Because our study was conducted under pharmaceutical rather than dietary-supplement regulations, agents identical to the ones we used may not be commercially available.

How should our results affect the treatment of symptomatic osteoarthritis of the knee? Our finding that the combination of glucosamine and chondroitin sulfate may have some efficacy in patients with moderate-to-severe symptoms is interesting but must be confirmed by another trial. In making therapeutic decisions, physicians and patients alike should be aware of our data suggesting that celecoxib has a much faster time to response than glucosamine, chondroitin sulfate, or the two in combination. Continuing research is needed to establish the potential efficacy and increase our understanding of the biology, pharmacology, and pharmacokinetics of these agents.

Supported by a contract from the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NO1AR92236).

Drs. Bingham, Brandt, Clegg, Hooper, and Schnitzer report having received consulting fees or having served on advisory boards for McNeil Consumer and Specialty Pharmaceuticals. Drs. Brandt, Moskowitz, Schnitzer, and Schumacher report having received consulting fees or having served on advisory boards for Pfizer. Dr. Brandt reports having equity interests in Pfizer. Drs. Moskowitz and Weisman report having received lecture fees from Pfizer; Dr. Brandt, lecture fees from McNeil Consumer and Specialty Pharmaceuticals; Drs. Bingham, Clegg, Hooper, Jackson, Molitor, Sawitzke, and Schnitzer, grant support from Pfizer; and Dr. Bingham, grant support from McNeil Consumer and Specialty Pharmaceuticals. Dr. Brandt reports having received royalties from books related to osteoarthritis. Dr. Moskowitz reports having served as an expert consultant for Pfizer. No other potential conflict of interest relevant to this article was reported.

We are indebted to McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, Pa., for donating acetaminophen; to Bioiberica, S.A., Barcelona, for donating sodium chondroitin sulfate; and to Ferro Pfanstiehl Laboratories, Waukegan, Ill., for donating a portion of the glucosamine hydrochloride through Wilke Resources.

APPENDIX

In addition to the authors, the following investigators participated in GAIT: National Center for Complementary and Alternative Medicine/National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Md. — S. Serrate-Sztein, E. Webster-Cissel; Steering Committee — N. Bellamy, G. Cannon, D. McClain, J. Sandy, A. Sawitzke, J. Theodosakis; University of Utah Coordinating Center, Salt Lake City — G. Cannon, J. Christensen, M. Finco, D. Kumeroski, M. Lewandowski, K. Mara, J. Mendivil, A. Sawitzke; Veterans Affairs (VA) Cooperative Studies Program Coordinating Center, Hines, Ill. — M. Abdellatif, D. Motyka, J. Motyka, T. Nydam, M. Reinhard; VA Cooperative Studies Program Pharmacy Coordinating Center, Albuquerque, N.M. — J. Barnhill, C. Fye, W. Gagne; University of Nebraska, Omaha — A. Burch, D. O'Grady; Case Western Reserve University, Cleveland — M. Hooper, M. Lesko; Indiana University, Indianapolis — D. Ang, R. Grau, H. O'Brien, B. Shultz, A. Schaffter; Hospital for Joint Diseases, New York — V. Abellana, P. Rosenthal; Cedars-Sinai Medical Center, Los Angeles — D. Silver, S. Choudry, K. Gilley, A. Guieliano, C. Joseph, A. Tiwari; University of Utah, Salt Lake City — K. Cooper, K. Fredley, A. Kim, A. Portmann, S. Smith; University of California, San Francisco, San Francisco — T. Munoz, N. Palmetto, R. Stuart-Thiessen, T. Solomon; Presbyterian Hospital, Dallas — E. Barnboym, J. Perla; University of Alabama, Birmingham, Birmingham — L. Heck, E. Coffey, M. Robertson, K. Woods; University of Pennsylvania, Philadelphia — J. Dinnella, H. Hannah, C. Shaw, C. Smith; University of Pittsburgh, Pittsburgh — S. Manzi, M. Graham, J. Jablon; Arthritis Research and Clinical Centers, Wichita, Kans. — T. Pryor, R. Schumacher, E. Sparr, K. Urbansky; Virginia Mason Medical Center, Seattle — C. Edwards, A. Mondt, E. Voon, K. Yim; University of Arizona, Tucson — C. Bush, J. Fuessler, J. Sonder; Northwestern University, Chicago — D. Czech, L. Robinson; University of California, Los Angeles, Los Angeles — D. Khanna, W. Chen, E. Hasan, L. Woolcock.

REFERENCES

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778-99.

2. United States Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Aging. Center for Disease Control's role in combating the burden of arthritis. Washington, D.C.: Department of Health and Human Services, 2004.

3. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. II. Osteo-

arthritis of the knee. Arthritis Rheum 1995;38:1541-6.
4. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;36:1196-206.
5. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991;325:87-91.
6. Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. N Engl J Med 2004;351:2767.
7. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092-102.
8. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352:1081-91.
9. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000;283:1469-75.
10. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
11. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum 1989;18:Suppl 2:14-7.
12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
13. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498-502.
14. Hochberg MC, Altman RD, Brandt KD, Moskowitz RW. Design and conduct of clinical trials in osteoarthritis: preliminary recommendations from a task force of the Osteoarthritis Research Society. J Rheumatol 1997;24:792-4.
15. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
16. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
17. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004;12:389-99.
18. SAS user's guide, version 8. Cary, N.C.: SAS Institute, 2000.
19. Annual nutrition industry overview. Nutrition Business J 2005;X:6-7.
20. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. J Rheumatol 1998;25:2203-12. [Erratum, J Rheumatol 1999;26:1216.]
21. Lehmann R, Brzosko M, Kopsa P, et al. Efficacy and tolerability of lumiracoxib 100 mg once daily in knee osteoarthritis: a 13-week, randomized, double-blind study vs. placebo and celecoxib. Curr Med Res Opin 2005;21:517-26.
22. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Arthritis Rheum 2000;43:978-87.
23. Schnitzer TJ, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in patients with osteoarthritis of the knee: a combined analysis of the VACT studies. J Rheumatol 2005;32:1093-105.
24. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. BMJ 2002;325:619.
25. Houpt JB, McMillan R, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. J Rheumatol 1999;26:2423-30.
26. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251-6.
27. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113-23.
28. Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Rheum 2004;51:738-45.
29. McAlindon T, Formica M, LaValley M, Lehmer M, Kabbara K. Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an Internet-based randomized double-blind controlled trial. Am J Med 2004;117:643-9.
30. Mazieres B, Loyau G, Menkes CJ, et al. Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis: 5-months result of a multicenter double-blind controlled prospective study using placebo. Rev Rhum Mal Osteoartic 1992;59:466-72. (In French.)
31. Conrozier T. Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6). Presse Med 1998;27:1862-5. (In French.)
32. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005;2:CD002946.
33. Adebowale AO Cox DS, Liang Z, Eddington ND. Analysis of glucosamine and chondroitin sulfate content in marketed products and the Caco-2 permeability of chondroitin sulfate raw materials. J Am Nutr Assoc 2000;3:37-44.
34. Joint remedies — glucosamine and chondroitin supplements appear to ease arthritis symptoms and possibly fight the disease itself: we tested 19 national products. Consum Rep 2002;67:18-21.
35. Russell AS, Aghazadeh-Habashi A, Jamali F. Active ingredient consistency of commercially available glucosamine sulfate products. J Rheumatol 2002;29:2407-9.