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The Effect of Glucosamine and/or Chondroitin Sulfate on the Progression of Knee Osteoarthritis: A GAIT Report

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Abstract

Objective—Osteoarthritis of the knee causes significant morbidity and current medical treatment is limited to symptom relief, as therapies able to slow structural damage remain elusive. This study sought to evaluate the effect of glucosamine hydrochloride (glucosamine, G), sodium chondroitin sulfate (chondroitin sulfate, CS) (alone and in combination), celecoxib and placebo on progressive loss of joint space width (JSW).

Methods—A double-blind twenty-four month placebo-controlled study conducted at nine sites in the United States enrolled 572 participants from Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) who satisfied radiographic criteria (Kellgren and Lawrence (K&L) Grade 2 or 3 changes and JSW of at least 2mm at baseline). Persons with primarily lateral compartment narrowing at any time point were excluded. Patients continued G 500mg three times daily, CS 400mg three times daily, the combination, celecoxib 200mg daily or placebo as randomized for GAIT. Minimum medial tibiofemoral JSW was measured at baseline, 12 and 24 months. The primary outcome measure was JSW change from baseline.

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Results—The average JSW loss at 2 years for placebo, adjusted for design and clinical factors, was 0.16mm. No statistically significant difference for any treatment group compared to the placebo group was observed. Treatment effects for K&L Grade 2 knees, but not K&L Grade 3 knees showed a trend toward improvement relative to placebo. The study's power was diminished by sample size, variance of JSW measurement and a smaller than expected loss in JSW.

Conclusions—At two years, no treatment achieved a predefined clinically important difference in JSW loss compared to placebo. However, patients with K&L Grade 2 osteoarthritis appear to have the greatest potential for modification by these treatments (ClinicalTrials.gov number, NCT00032890).

Introduction

Osteoarthritis (OA) is the most common form of arthritis, affecting at least 20 million Americans and it's prevalence is expected to double over the next two decades (1,2). Once considered the consequence of aging, OA is now thought to involve a complex interaction of biologic and pathologic processes influenced by a number of factors, including genetics, age, gender, obesity, joint injury, and muscle strength (3) together with mechanical factors such as repetitive microtrauma and instability (4). Although the pathogenesis of OA has yet to be clearly defined, failure of articular cartilage is central to disease development (5).

Loss of cartilage in OA is usually assessed as a radiographic interbone distance. Precision and reproducibility in the measurement of this distance are improved by application of standardized acquisition protocols. Each protocol attempts to address difficulties inherent in obtaining reproducible positioning and projection of the joint. At the inception of this study, both anteroposterior (AP) and posteroanterior (PA) projection protocols using various degrees of knee flexion with or without fluoroscopic guidance of positioning were under scrutiny (6–12). Fluoroscopy was not commonly employed due to limited availability, difficulty in achieving and maintaining technician training and the need to minimize cost and radiation exposure. Using available approaches, a narrowing of approximately 0.25mm per year was observed and reported (9). The metatarsophalangeal (MTP) view of Buckland-Wright, a PA directed flexed knee view, was thought to have a balance of ease, thrift and precision adequate to detect the anticipated change in joint space width (JSW) over the two year study (10).

When the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)(13) was initiated, efficacy with glucosamine hydrochloride (glucosamine, G) and sodium chondroitin sulfate (chondroitin sulfate, CS) in the symptomatic treatment of knee OA had been suggested (14,15). Almost all available studies had evaluated them singly despite the fact that they were commonly marketed in combination, especially in the United States. In addition, radiographic studies were in progress evaluating the effect of G or CS on JSW narrowing (16–18). The reported benefit observed in these studies remains controversial due in part to methodological concerns. The trial herein reported is a prospective study of GAIT enrollees to evaluate whether G or CS, taken alone or in combination for two years, could be demonstrated to have a structure-modifying effect in OA of the knee. The primary endpoint was change in minimum medial tibiofemoral JSW measured on films obtained using the standardized Buckland-Wright non-fluoroscopic MTP radiographic protocol (10).

Methods

Study design

Nine of the sixteen GAIT centers participated in the structural study: the Arthritis Research Center, Wichita; University of Arizona; Case Western Reserve University; Cedars-Sinai

Medical Center; Indiana University; University of California, Los Angeles; University of California, San Francisco; University of Pittsburgh; and the University of Utah. Eligible patients were at least 40 years old, had knee pain for at least six months and on the majority of days in the month preceding their enrollment in GAIT and had Kellgren and Lawrence (K&L) Grade 2 or 3 OA on a screening standing AP radiograph (19). If both knees from an individual qualified, both were evaluated for structural change over time. Qualifying patients received their blinded study treatment for a total of 24 months. Blinded study treatment consisted of glucosamine hydrochloride (G) 500 mg 3 times daily, sodium chondroitin sulfate (CS) 400 mg 3 times daily, the combination of G+CS, placebo, or celecoxib 200 mg daily.

Persons who had concurrent medical conditions that could confound evaluation of the knee joints or disease that would limit their successful completion of the trial were not eligible. Specific knees were excluded from evaluation if they had; 1) a minimum baseline medial JSW < 2 mm, 2) predominant lateral compartment osteoarthritis on any MTP film, and 3) a history of significant trauma or surgery to the knee. The protocol was approved by each site's IRB and all participants provided written informed consent.

It was estimated that 791 patients would be eligible to participate at the 9 centers and that the missing data rate would be 40%. The change in JSW at two years while taking placebo was expected to be 0.4 mm (9), with a standard deviation of 0.388 mm. A reduction in JSW loss from placebo of 0.2mm over two years was felt to be clinically meaningful. Hence, the study was designed to have 86% power with alpha set at 0.0125 for each of four comparisons using 95 persons in each group.

Radiographic technique

All radiology technicians selected to participate in this trial were experienced musculoskeletal radiology technicians. Technicians from each site were trained at a two-day session by Professor Buckland-Wright to perform standing non-fluoroscopic MTP radiographs (10). Technicians were also given a training and reference manual, and quick reference sheet. Centers notified the National Coordinator Center (NCC) when a change in radiology technicians occurred. New technicians received training by the already trained technologist on site. Documentation of technologist training was maintained by the NCC. Subjects had MTP radiographs obtained at baseline, 12 and 24 months. Per protocol, a foot map (placement of the subjects feet on a paper template on which an outline of the initial placement of the feet had been traced) was used to maintain similar positioning when obtaining repeat images. Over the course of the study, sites increasingly used digital image capture followed by film printing. All films were mailed to the central radiology center where they were assessed for quality, including labeling, alignment of the x-ray beam, positioning of the knees on the film, and x-ray beam penetration by two readers (see acknowledgements). Whenever indicated, repeat films were requested. Approved films were assigned a randomized code from a printed table in the order they were received, digitized using a Lumisys 75 scanner® and stored as 10 data bits archived in 16bit DICOM files using OSIRIX software (20).

One observer (ADS) used the Mdisplay program of Buckland-Wright to measure minimal medial joint compartment JSW on coded films. The program required the user to mark the endpoints of the tibial and femoral condyles and then interpreted the joint boundary before searching for the minimum JSW. Standard procedures assured that the program did not measure osteophytes or disparate locations for a series of films. Series were read together, but film sequence and treatment group remained masked. The standard error for the use of the Mdisplay was 0.025mm. In order to estimate the error associated with the process of measurement, knees from 41 cases likely to have little or no progression over a one-year

period were used (knees graded as K&L 0 or 1). The within knee SD error of repeated measurements showed an estimated precision error of 0.16mm.

Outcomes

The primary outcome of the trial was the mean change in JSW in the medial compartment of the knee over 2 years assessed on films obtained using the Buckland-Wright non-fluoroscopic MTP protocol, and read using computer generated measurements from digitized images.

The secondary outcome was the percentage of progressors at two years, defined as knees with a loss in JSW that exceeded 0.48 mm (three times the SD of error of measurement) when compared to baseline, consistent with approaches used by other studies (8,18,21–23).

Statistical Analysis

All analyses were done on a modified intention-to-treat basis. Baseline characteristics were compared across groups using a chi-square test for categorical variables and analysis of variance for continuous variables. Statistical testing of treatment differences was adjusted for the comparison of each of 4 treatments with a control (placebo) using multivariate t-statistics (analogous to Dunnet's t-test) to calculate 95% confidence intervals (CI) (24). A 95% CI that excludes zero would indicate a statistically significant result. The analysis sample of 357 persons contributing 581 knees had 55% power to detect the prespecified clinical difference in JSW change of 0.2mm allowing for an overall type 1 error rate of 5% using 4 treatment comparisons with placebo based on a Dunnet t-test.

The primary longitudinal analysis compared the mean change in JSW over two-years of each intervention group to placebo while controlling for design factors (weeks on treatment, elapsed time from baseline X-ray, recruitment site) and clinical factors (baseline JSW, gender, baseline pain, disease duration, normal/overweight/obese weight status, K&L Grade) using the knee as the unit of analysis. A mixed-effects regression model using SAS 9.1® was employed to validly compare each treatment group with the placebo, accounting for repeated measures over time and for clustering due to the monitoring of both knees for some individuals. This widely accepted form of repeated measures analysis utilizes all data collected on this cohort. Sensitivity analyses used mixed-effects regression to separately test for treatment differences at 1- and 2-years.

Secondary longitudinal analysis compared the occurrence of disease progression for JSW loss exceeding 0.48mm over the two-year follow-up for each intervention group as compared to placebo while controlling for all the above factors. Again, the knee was the unit of analysis. Logistic regression employed generalized estimating equations (GEE) implemented with SAS 9.1® to validly analyze repeated measures over time and account for clustering due to monitoring of both knees.

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Results

Baseline characteristics

The flow of the 662 patients who consented and contributed data are shown in Table 1 within the groups to which they had been randomized for GAIT. The 5 groups entered without significant differences. One hundred seventy-one patients who withdrew prior to the

first follow-up radiograph are shown as withdrawals. Films for which change in JSW could not be accurately measured were rejected for quality and accounted for most of the 44 technical losses. The final sample included 357 persons and 581 qualifying knees with baseline and at least 1 follow-up MTP film that met radiographic criteria. The assessable patients were similar to the eligible patients except that significantly more females were in the eligible group. Sixty-six percent of patients contributed two knees to the analysis. The study sample was 63.6% female, with mean age 56.9(9.8) years and mean body mass index 32(6.9) kg/m^2. There also were no significant differences in the baseline characteristics across the placebo and treatment groups among assessable patients (Table 2), nor were appreciable differences seen between this population and all participants in GAIT.

Primary outcome

There were no significant treatment differences in JSW loss over two years (Table 3) compared to placebo using mixed-model regression analysis, the G group had the least average loss (0.013mm at 2 yrs); while the G + CS group had the greatest average loss (0.194mm at 2 yrs). One design and one clinical covariate were significant predictors of JSW loss from baseline; JSW loss was greater for K&L Grade 3 than K&L Grade 2 knees and increased with time, (i.e. greater at year 2 than year 1). Sensitivity analyses performed to evaluate JSW using only one knee per patient at 1- and at 2- years yielded nearly identical results as the main analysis. . The unadjusted mean placebo JSW loss was substantially less (0.34mm) in the placebo group than anticipated by the study design (0.40mm loss over two years), while it was 0.273mm for K&L Grade 2 and 0.523mm for K&L Grade 3 placebo treated knees.

Secondary outcome

Compared to placebo, the odds of progression for any group were not significant (Table 4). Radiographic progression (JSW loss exceeding 0.48mm) was most frequent in the group treated with the combination of G + CS (24.4% at 2 years), while progression was least frequent in the G group (18.6% at 2 years). The overall order of progression across treatment groups paralleled that seen for mean JSW loss.

Figure 1 shows difference in JSW loss compared to placebo by treatment group, stratified by K&L Grade and adjusted for design and clinical factors. Although not statistically significant, all treatment groups show numerically less JSW loss than placebo in K&L Grade 2 knees but more JSW loss compared to placebo in K&L Grade 3 knees. This effect of K&L Grade on treatment is further examined in Figure 2, where the estimated odds ratio of progression compared to placebo is less than 1 for all treatment groups in K&L Grade 2 knees, while it is greater than 1 for all treatments for K&L Grade 3 knees. The overall pattern of treatment effect is remarkably constant in the two K&L Grade subsets for both JSW loss (Figure 1) and progression of osteoarthritis (Figure 2).

Discussion

This study assesses radiographic outcomes in OA of the knee in persons using G, CS, G +CS, celecoxib, or placebo. Over two years, no treatment achieved the study's predefined clinically important difference from placebo in terms of JSW loss. The power was limited by smaller than anticipated sample size and increased variability of measurement.

Controlled studies have reported slowing of JSW loss using G (17,18). In particular, the study by Reginster and colleagues followed 106 G treated and 106 placebo patients (18). The mean JSW losses were 0.06mm and 0.31 mm respectively. When they defined progression as loss >0.5mm, twice as many progressors were observed in the placebo treated

group as in the G treated group. A randomized trial by Pavelka et al examined 101 G and 101 placebo treated patients over three years (17). They found a mean JSW *increase* of 0.04mm with G treatment and a decrease of 0.19mm on placebo therapy, respectively (17). A meta-analysis performed by Richy summarized these studies with respect to JSW loss and found an effect size of 0.41 SD units when treated with G (25). Our G group had 0.153mm less loss over two years as compared to placebo for a smaller effect size of 0.25 SD units (26). In part, this may be related to the increased variability associated with multi-center trials.

Similar approaches have been used to examine the effect of CS on JSW loss (16,27–30). A meta-analysis performed by Reichenbach summarized minimum JSW loss data from 5 trials that included treatment with CS. They found an average effect size of 0.18 SD units, a size not clearly felt to be of clinical significance (31). In our study, the CS group had an even smaller effect size of 0.10 SD units with 0.059mm less JSW loss at two years.

No prior reports have examined the combined effects of G and CS on JSW loss, even though this is a combination commonly taken by patients. Our study observed similar JSW loss in the combination group compared to placebo, but the loss was greater than that seen with G or CS alone, raising the possibility of interference associated with their combined use. Pharmacokinetic studies have shown decreased absorption of G when given concurrently with CS (Jackson, CG-unpublished data), which could effectively lower the G blood levels obtained. Alternatively, the higher proportion of K&L 3 Grade subjects who were treated with combination therapy might have altered the results; in general K&L 3 subjects demonstrated more progression and may have had less treatment benefit (Figure 1 and Figure 2). Celecoxib might have been predicted to progress more than placebo as previous nonsteroidal anti-inflammatory agent trials have suggested increased JSW loss occurs with their use (32), however, other trials have not (33,34). No significant difference between the celecoxib group and placebo was observed in this trial and the direction of the changes was in line with those seen with G or CS.

While the optimal method of documenting disease progression in OA is unknown, the standard at present remains measurement of JSW on plain radiographs (35–39). Many feel that MRI may replace radiographs (40) in the future, especially if the substantial costs of MRI can be offset by a reduction in the required sample size and trial duration due to enhanced precision and sensitivity. When this study was designed, it was felt that weight-bearing PA based films had the best overall performance characteristics. Fluoroscopic guidance for placement was not used due to cost and the difficulty of standardization in a multi-center trial. The non-fluoroscopic MTP view of Buckland-Wright was chosen to balance these issues and was considered adequate to detect a clinically important difference at two years of follow-up (10,12,41). In the time since the initiation of this trial, fluoroscopic methods have been tested, validated and (35–37,42–44) may now be considered more advantageous, (45) (39) even in multi-center trials, as they allow increased sensitivity to detection of JSW loss due to better alignment of the tibial plateau (6,38,43,46).

In this study, the rate of JSW loss over 2 years was less than the conservative estimate of 0.20mm loss per year using the radiographic technique available at the time of study design (9). Other recent large studies have also demonstrated significantly less loss. For example, Michel et al found JSW losses close to 0.1mm/year (16) and the risedronate trial using a fluoroscopically aligned MTP view demonstrated a placebo group loss of only 0.088mm per year in the European and 0.13 in the North American arms, respectively (21). These results are even less than the 0.14mm annual loss observed in our placebo treated arm. It is likely that the expected rate of loss differs due to radiographic technique and is affected by quality of alignment of the tibial plateau, with better alignment associated with improved detection

of JSW loss (39,43). Overall, it appears that a rate of progression of 0.1mm/year should be used for planning of future OA radiographic progression studies.

Since a substantial number of individuals may experience little or no JSW loss, mean loss may not even be the best measure to compare treatment groups (35,37). As with other trials (18,23), we defined progressors as those who lost more than three times the average SD of error of measurement. Although we had a greater proportion of progressors using this definition (22.4%) than reported in the placebo group of the risedronate study (14%), this was not statistically different from placebo in our study. Overall, the order of effect was similar to that observed for the mixed-model mean JSW loss results.

Although the use of state of the art statistical methodology allowed us to utilize all the collected data to obtain the most robust estimates of treatment effect possible, the power of this study was limited by several factors. First, the number of qualifying individuals with acceptable follow-up films was less than expected (14.1%. loss to this effect rather than the expected of 3–10%) (35). Second, the magnitude of JSW loss in the placebo group was less than anticipated from the literature at the time (0.14mm/year versus 0.2mm/year)(9). Third, the variability of JSW measurement was larger than expected (0.16 versus 0.09 from available literature) (11,12). The standard deviations of JSW measurement for the MTP view were 2–3 times the measured JSW difference in this study which compares favorably to other examinations of this technique (12) but is higher than the data available at the time the study was designed. Although these factors limit the power of the present study, the results do provide valuable information for future OA study design.

In summary, no therapy reached predefined thresholds for either statistical or clinically meaningful structural modification. The combination of G + CS may be less active compared to their individual effects. The validity and mechanism of this novel observation is uncertain but could be related to altered G absorption. In future OA trials evaluating structural modification, K&L Grade 2 knees may represent a more potentially responsive population, however, a larger sample size, longer study duration, and/or improved methods of measurement will be required as the rate of JSW loss seen on plain radiographs is much slower than previously appreciated.

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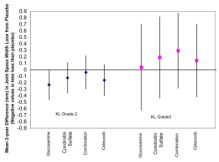

Figure 1.

Treatment effect relative to placebo for JSW loss stratified by Kellgren and Lawrence Grade. Adjusted mean two-year loss in joint space is shown for 357 subjects and 581 knees. JSW-Joint space width.

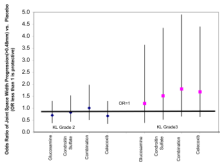

Figure 2.

Treatment versus placebo Odds Ratio for JSW progression (>0.48mm) by Kellgren and Lawrence Grade. Data from 357 subjects and 581 knees are shown here as a odds ratio of progression. JSW-Joint space width.

Table 1

Study Patient Flow

CONSENTED WITH DATA (Patients)	Glucosamine 134	Chondroitin Sulfate 123	Combination 128	Placebo 134	Celecoxib 143
ELIGIBLE*	119	107	110	114	122
WITHDREW†	33	30	40	36	32
TECHNICAL LOSSES‡	9	6	11	8	10
ASSESSABLE	77	71	59	70	80
KNEES	123	116	94	113	135
Single knee	31	24	25	27	25
Both	46	46	34	43	55

*Patients with Kellgren and Lawrence grade 2 or 3 and joint space width >= 2mm

†Patients who withdrew prior to the first followup radiograph

‡Patients whose film quality did not allow joint space width loss measurement

Table 2

Baseline Characteristics of the Structural Study by Group

	Glucosamine	Chondroitin	G+C	Celecoxib	Placebo	Structural	GAIT
Subjects (N)	77	71	59	80	70	357	1583
Age in years, mean (SD)	56.7 (10.4)	56.4 (9.2)	56.5 (9.9)	58.3 (10.7)	56.6 (8.4)	56.9 (9.8)	58.6 (10.3)
HAQ Pain Scale, mean (SD)	46.4 (20.2)	51.6 (18.4)	51.3 (18.4)	52.2 (19.9)	52.3 (19.2)	50.7 (19.3)	54.1 (20.4)
Years duration OA symptoms mean (SD)	9.2 (9.4)	8.8 (8.9)	10.5 (9.8)	10.3 (9.5)	9.4 (8.7)	9.6 (9.2)	10.0 (9.8)
Percentages							
Females	61.0	71.8	55.9	63.8	64.3	63.6	64.1
BMI <25	13.0	14.1	11.9	16.3	4.3	12.0	14.2
BMI 25–30 Overweight	28.6	39.4	35.6	31.3	40.0	34.7	33.8
BMI >30 Obese	58.4	46.5	52.5	52.5	55.7	53.2	51.9
Knees (N)	123	116	94	135	113	581	
KL 2 (%)	80.5	81.0	69.2	72.6	80.5	76.9	
KL 3 (%)	19.5	19.0	30.9	27.4	19.5	23.1	
Mean of JSW (mm)	4.04 (1.01)	3.86 (0.90)	4.04 (0.96)	4.01 (1.01)	4.07 (0.93)	4.00 (0.96)	
Median of JSW (Interquartile range) (mm)	3.95 (3.36, 4.60)	3.90 (3.28, 4.41)	3.97 (3.33, 4.82)	4.01 (3.21, 4.60)	4.02 (3.51, 4.60)	3.95 (3.33, 4.60)	

Table 3

Loss in JSW Over 2 Years Observation by Treatment Group

Therapy	Number Subjects	Unadjusted Average 2yr joint space width Loss (mm)	Average 2yr joint space width Loss (mm)*	Difference from Placebo†	95% CI for the difference
Glucosamine	77	0.206	0.013	−0.153	[−0.379,0.074]
Chondroitin Sulfate	71	0.250	0.107	−0.059	[−0.287,0.169]
Glucosamine + Chondroitin Sulfate	59	0.435	0.194	0.028	[−0.214,0.271]
Celecoxib	80	0.305	0.111	−0.055	[−0.279,0170]
Placebo	70	0.341	0.166		

*Adjusted for baseline joint space width, gender, weight, K&L Grade, weeks on treatment, follow-up X-ray time, site. From mixed model - 581 knees contributed by 357 people.

†Negative value is less loss than placebo

Table 4

Disease Progression Over 2 Years Observation by Treatment Group (>0.48mm)

Therapy	N Subjects	% Progression*	Odds ratio compared to Placebo†	95% CI for the odds ratio
Glucosamine	77	18.6	0.79	[0.48,1.3]
Chondroitin Sulfate	71	21.4	0.94	[0.57,1.55]
Glucosamine + Chondroitin Sulfate	59	24.4	1.12	[0.67,1.88]
Celecoxib	80	20.2	0.87	[0.53,1.43]
Placebo	70	22.4		

*Adjusted for baseline joint space width, gender, weight, K&L Grade, weeks on treatment, follow-up X-ray time, site. From mixed model - 581 knees contributed by 357 people.

†Negative value is less loss than placebo