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Potential effects of chondroitin sulfate on joint swelling: a GAIT report

M. C. Hochberg M.D., M.P.H.†‡* and D. O. Clegg M.D.†‡

† *University of Maryland School of Medicine, 10 S. Pine Street, MSTF 8-34, Baltimore, MD 21201, United States*

‡ *University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132, United States*

Summary

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was a randomized double-blind placebo and active comparator (celecoxib) controlled trial of 1583 persons with symptomatic osteoarthritis (OA) of the knee[1]. Patients randomized to celecoxib had significant improvement in knee pain compared to those randomized to placebo. No statistically significant improvement in knee pain compared to placebo was seen among patients randomized to the dietary supplements, although a subset of patients with moderate-to-severe knee pain at entry who were assigned to the combination of glucosamine and chondroitin sulfate did seem to experience some improvement. Additionally, patients taking chondroitin sulfate were noted to have a statistically significant improvement in knee joint swelling. An exploratory *post hoc* analysis of GAIT patients suggested the effect of chondroitin sulfate on joint swelling occurred more often in patients with milder pain and lower Kellgren–Lawrence Grade at entry.

Key words: Osteoarthritis, Glucosamine, Chondroitin.

GAIT was a 24-week, double-blind randomized placebo-controlled trial comparing glucosamine, chondroitin sulfate, and the two in combination in treating knee pain in patients with clinical and radiographic knee osteoarthritis[1]. GAIT was funded by the National Institutes of Health with the Coordinating Center at the University of Utah in Salt Lake City, the Data Repository in Hines, Illinois and the Pharmacy Center in Albuquerque, New Mexico. There were 16 participating clinics that were affiliated with academic rheumatology centers across the United States. GAIT patients were required to have symptomatic (knee pain $\geq$6 months; WOMAC pain 125–400 mm) and radiographic (Kellgren and Lawrence Grades 2 or 3) criteria for diagnosis of knee osteoarthritis. GAIT patients were randomized into one of five arms: placebo, glucosamine 500 mg three times daily, chondroitin sulfate 400 mg three times daily, combination glucosamine plus chondroitin sulfate in the same dosages or celecoxib 200 mg daily. All patients were allowed to use acetaminophen up to 4 g daily for rescue analgesia. Study agents were mandated to be of pharmaceutical grade by the study sponsor so the study was conducted under an Investigational New Drug application from the federal Food & Drug Administration[2]. In order to ensure a balanced distribution among predetermined pain subgroups, the randomization was stratified by both baseline WOMAC pain score where "mild" pain patients were defined as WOMAC 125–300 mm and "moderate-to-severe" defined as 300–400 mm. The primary outcome measure selected *a priori* was the summed WOMAC pain subscales defined by visual analog scales. Only patients with summed scores 125–400 mm qualified and responders were defined as having 20% or greater improvement at 24 weeks compared to baseline.

Subsequent to the development of GAIT, a predefined response measure that assesses both absolute and relative improvement in both WOMAC pain and function domains was proposed by OMERACT-OARSI[3]. Due to the fact that each of the domains of the OMERACT-OARSI response criteria set had been collected prospectively; OMERACT-OARSI Response was defined as a secondary outcome measure.

Over 3000 patients were screened for recruitment to GAIT and 1583 patients were randomized (Fig. 1). There were no baseline differences among the randomized treatment groups (Table I). The mean age of the study population was 58.6 years; almost two-thirds (64%) were women. The mean BMI was 31.7 kg/m^2. The patients had had osteoarthritis for a mean of 10 years and 44.7% had Kellgren and Lawrence grade 3 changes on knee radiographs. Over one-quarter (26.9%) of patients had joint swelling at entry in the study; the prevalence of joint swelling across the treatment groups was similar and ranged from 24.9% in the glucosamine group to 28.3% in the chondroitin sulfate group.

Table II details baseline disease severity; GAIT patients had a mean of WOMAC pain score of 236 mm; mean WOMAC stiffness score of 106 mm and mean WOMAC function score of 772 mm. The mean Health Assessment Questionnaire (HAQ) at entry was 0.78. No differences were seen among the five treatment groups.

Table III outlines response to the study agents; celecoxib compared to placebo demonstrated a statistically significant improvement ($P = 0.008$) in the primary outcome measure. A trend toward improvement was also seen in the glucosamine/chondroitin sulfate combination group ($P = 0.09$). Similarly, statistically significant improvement was seen among OMERACT-OARSI Responders in the celecoxib

*Address for correspondence and reprint requests to: Marc C. Hochberg, University of Maryland School of Medicine, 10 S. Pine Street, MSTF 8-34, Baltimore, MD 21201, United States. Tel: 1-410-706-6474; Fax: 1-410-706-0231; E-mail: mhochber@umaryland.edu

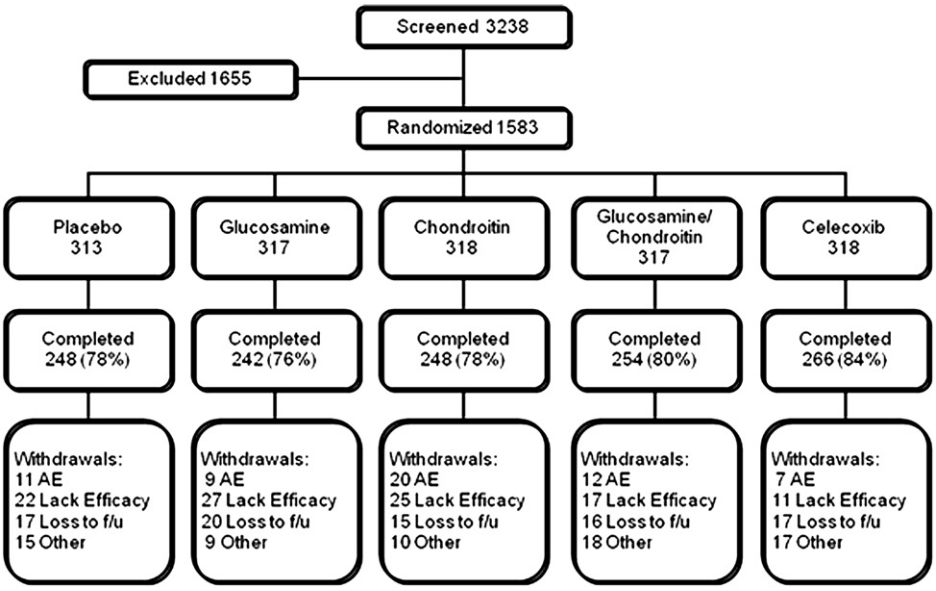

Fig. 1. GAIT recruitment and follow-up.

($P = 0.007$) and combination ($P = 0.02$) groups. This observation in the combination group was more striking in the predefined subgroup with moderate-to-severe WOMAC pain at entry (Table IV).

Another interesting observation from GAIT was noted in patients who were found to have joint swelling at entry into the trial. Joint swelling was determined by the investigator as present or absent at study initiation and completion. In patients noted to have joint swelling, the swelling improved significantly in patients that received chondroitin sulfate compared to patients who received placebo. A *post hoc* analysis was undertaken to further assess this observation. Significant statistical interaction existed in both Kellgren and Lawrence Grade and WOMAC stiffness and function subscales. These findings suggest that patients with Kellgren and Lawrence Grade 2 radiographic changes were substantially more responsive to the potential salutary effects of chondroitin sulfate than those with Kellgren and Lawrence Grade 3 changes. Further, improvement was more likely to occur in the chondroitin sulfate treated patients with lower WOMAC function and stiffness scores and a numerical trend was seen also in patients with lower WOMAC pain scores.

Adverse events were captured regardless of their relatedness to agents. Serious adverse events were seen in less than 4% of patients; specifically there were no deaths, nonfatal myocardial infarctions or GI bleeds. One patient taking celecoxib had a cerebrovascular accident and two patients had transient ischemic attacks (one taking celecoxib and one

Table I
Patient baseline characteristics

Characteristic	All patients
N	1583
Age − yrs	58.6
Female − %	64
BMI − kg/m^2	31.7
OA Sx − yrs	10.0
KL 3 − %	44.7
Joint swelling − %	26.9

Table II
Baseline disease severity

Outcome	All patients	WOMAC 125−300	WOMAC 301−400
WOMAC pain	236	206	341
WOMAC stiffness	106	97	138
WOMAC function	772	684	1078
HAQ	0.78	0.72	0.98

Table III
Overall response

Treatment group	*N*	20% Pain (%)	OMERACT-OARSI (%)
Placebo	313	60.1	56.9
Glucosamine HCl	317	64.0	60.6
Chondroitin sulfate	318	65.4	63.5
G + CS	317	66.6	65.6
Celecoxib	318	70.1	67.3
G + CS vs placebo		$P = 0.09$	$P = 0.02$
Celecoxib vs placebo		$P = 0.008$	$P = 0.007$

Table IV
Response of "moderate-to-severe" pain subgroup

Treatment group	*N*	20% Pain (%)	OMERACT-OARSI (%)
Placebo	70	54.3	48.6
Glucosamine HCl	70	65.7	65.7
Chondroitin sulfate	70	61.4	58.6
G + CS	72	79.2	75.0
Celecoxib	72	69.4	66.7
G + CS vs placebo		$P = 0.002$	$P = 0.001$
Celecoxib vs placebo		$P = 0.06$	$P = 0.03$

glucosamine). Because of the concern for the effects of selective Cox 2 inhibitors on cardiac function this was specifically assessed. There was no evidence of an increase in ischemic cardiac events, although there was a significantly elevated incidence of palpitations, atrial fibrillation and increased blood pressure. With regard to laboratory investigations, increased blood glucose levels were observed across all groups.

In conclusion, GAIT patients treated with celecoxib exhibited significant improvement in osteoarthritis knee pain. GAIT was hindered by the high placebo response rate that was observed (60.1%) which could have limited the ability to detect clinical response. In the moderate-to-severe pain group there did appear to be changes; however, the sample size of that group was relatively small impacting the robustness of those findings. Chondroitin sulfate treated patients demonstrated a statistically significant improvement in joint swelling compared to placebo treated GAIT patients.

Further, an exploratory *post hoc* analysis of those chondroitin sulfate treated patients suggested that patients with relatively earlier disease as indicated by relatively milder symptoms and baseline Kellgren and Lawrence Grade 2 radiographic changes seemed most likely to benefit from chondroitin sulfate treatment.

Conflict of interest

Dr. Hochberg is a consultant to BioIberica SA. Dr. Clegg has no relationship to disclose.

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