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Symptomatic Effects of Chondroitin 4 and Chondroitin 6 Sulfate on Hand Osteoarthritis

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial at a Single Center

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Objective. **To evaluate the symptomatic effects of highly purified chondroitin 4 and chondroitin 6 sulfate (CS) therapy in patients with osteoarthritis (OA) of the hand.**

Methods. **This investigator-initiated, single-center, randomized, double-blind, placebo-controlled clinical trial included 162 symptomatic patients with radiographic evidence of hand OA (American College of Rheumatology criteria). Inclusion criteria included patient's assessment of global spontaneous hand pain of at least 40 mm on a 0–100-mm visual analog scale (VAS) and functional impairment of at least 6 (0–30 scale) on the Functional Index for Hand OA (FIHOA) in the most symptomatic hand. Patients received either 800 mg of CS (n = 80 patients) or placebo (n = 82 patients) once daily for 6 months and were analyzed in an intent-to-treat approach. The two primary outcomes were the change in the patient's assessment of global spontaneous hand pain and in hand function (by FIHOA score) from baseline to month 6. Secondary outcomes were improvement in grip strength, duration of morning stiffness, acetaminophen consumption, and the investigator's global impression of treatment efficacy.**

Results. **There was a significantly more pronounced decrease in the patient's global assessment of hand pain in the CS group than in the placebo group (difference VAS scores −8.7 mm; $P = 0.016$). Hand function improved significantly more in the CS group than in the placebo group (difference in FIHOA scores −2.14; $P = 0.008$). There was a statistically significant between-group difference in favor of CS for the duration of morning stiffness and for the investigator's global impression of treatment efficacy. Changes in grip strength, acetaminophen consumption, and safety end points were not significantly different between the two groups.**

Conclusion. **This study demonstrates that CS improves hand pain and function in patients with symptomatic OA of the hand and shows a good safety profile.**

Osteoarthritis (OA) is a degenerative disorder that primarily affects the articular cartilage and causes painful disease flares and disability in activities of daily living. In developed countries, OA is the most common form of arthritis, resulting in a significant impact on medical expenses, both in terms of direct and indirect medical costs (1). Hand OA is present in ~20–30% of adults (2,3), with age-related increases, reaching a prevalence of >50% after the age of 60 years (4,5). The most frequently affected joints are the distal interphalangeal (DIP), proximal interphalangeal (PIP), thumb interphalangeal, and trapeziometacarpal joints (6).

Despite its high prevalence and its impact on quality of life (7), the therapeutic options in hand OA are still limited. Clinical trials examining the efficacy of therapeutic approaches to hand OA specifically are scarce (8–10). Thus, management of hand OA has been

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largely extrapolated from the knowledge obtained in other forms of OA (11). The findings of one randomized controlled trial (RCT) that included a limited number of patients with hand OA supported the effect of an education program combined with exercise on joint function (12). Both oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated significant efficacy as compared to placebo in randomized controlled clinical trials (13,14). While acetaminophen has not been formally evaluated in hand OA, it has been recommended (11). Topical capsaicin was found to be superior to a placebo cream for treatment of pain and tenderness (15). Disease-modifying antirheumatic drugs, such as hydroxychloroquine and tumor necrosis factor antagonists, have been evaluated in a limited number of patients with erosive hand OA, with modest positive effects (16,17).

The only report of a RCT comparing chondroitin sulfate to a placebo for the treatment of hand OA described 2 independent trials, one with chondroitin sulfate and one with chondroitin polysulfate (18). After a followup of 3 years, OA structural damage was less pronounced in both active treatment groups. Furthermore, fewer patients from both chondroitin sulfate– and chondroitin polysulfate–treated groups developed "erosive" OA. However, no data on symptoms and function were reported, and so the clinical relevance of these radiographic findings remains unclear. Despite the good safety profile of chondroitin sulfate, the level of evidence for its efficacy in hand OA is low, as pointed out in the recent European League Against Rheumatism recommendations for the management of hand OA (11). Thus, we decided to conduct a clinical trial to examine the effects of chondroitin sulfate on signs and symptoms of hand OA.

PATIENTS AND METHODS

Study design and selection of patients. The Finger Osteoarthritis Chondroitin Treatment Study (FACTS) was an investigator-initiated, single-center, randomized, double-blind, placebo-controlled clinical trial. The study patients were recruited at the local rheumatology outpatient clinic and through advertisements in local newspapers. Patients were of either sex, ages 40 years and older, and fulfilled the American College of Rheumatology (ACR) criteria for the classification of hand OA (19). In addition, radiographic features of hand OA affecting at least 2 joints of the target hand on standard plain films obtained within 6 months of enrollment, as well as at least 2 painful flares of OA in the finger joints during the previous 12 months were required. We defined the target hand as the patient's most symptomatic hand or, when both hands were equally painful, the patient's dominant hand. To be eligible for study, the patients had to present with symptomatic OA. The minimal level of symptoms was joint pain of at least 40 mm on a 0–100-mm visual analog scale (VAS) and a Functional Index for Hand OA (FIHOA) score of at least 6 in the target hand (0–30 scale) (20).

The major exclusion criteria were any inflammatory joint disease of other origin, septic arthritis, previous articular fracture of the concerned joints, monarticular posttraumatic OA of the finger, a history of or the presence of any other rheumatic diseases that could cause secondary OA, severe comorbidity, intraarticular injection or articular lavage in a hand joint during the previous 3 months, treatment with corticoids by any route of administration during the previous month, planned surgery of the hands within the following 6 months, treatment with symptomatic slow-acting drugs (such as chondroitin sulfate, glucosamine, diacerein, and hyaluronic acid) during the 3 months preceding enrollment. Physical therapy was not allowed during the study period.

The study was approved by the Ethics Committee of the University Hospitals of Geneva. All patients gave their written informed consent to participate prior to inclusion into the study. This study was registered (ClinicalTrials.gov, unique identifier NCT00291499) prior to the enrollment of patients and was conducted in accordance with the principles of the Declaration of Helsinki.

Treatment intervention. Patients fulfilling the inclusion criteria were randomized to receive a single 800-mg tablet of chondroitin sulfate (CS) (Condrosulf; IBSA) or an identical placebo each day (taken with a glass of water) for a total period of 6 consecutive months. The Condrosulf prescription preparation contains highly purified chondroitins 4 and 6 sulfate of fish origin in a concentration of not less than 95%. This product has been approved in many European countries as a prescription treatment for OA at a daily dose of 800 mg.

For rescue analgesia, patients were allowed to take acetaminophen, 500-mg tablets, at a maximum dosage of 4 gm/day. Patients recorded their use of rescue medication in a diary. Patients were required to stop the analgesic treatment 24 hours before every symptom assessment, and washout of all analgesics and NSAIDs was required for an entire week prior to randomization. NSAIDs or glucocorticoids were not allowed, with the exception of 100 mg of acetylsalicylic acid per day for the prevention of cardiovascular events. Compliance with the study treatment was established by asking the patients about missed doses and by counting unused study drug tablets.

Treatment assignment. A randomization list was generated by a computer in blocks of 4 containing 2 placebo and 2 CS allocations. Patients were assigned a randomization number according to the order of inclusion. Patients, nurses, the medical team in charge of the patient, the physician performing the assessments, and the statistician performing the analysis were blinded to the treatment allocation. The treatment allocation was concealed in sealed envelopes until the end of the study.

Outcome measures. Clinical assessments were performed 7 days before enrollment (screening visit), at the time of enrollment (baseline; visit 0), and 1, 3, and 6 months after enrollment. Patients not taking any analgesics during the week before screening could be randomized during the same visit.

The primary outcome criteria were the change in the patient's assessment of global spontaneous hand pain on a

VAS and in hand function on the FIHOA score from baseline to month 6 (20). These outcome measures were assessed at baseline and at each followup visit. Global spontaneous hand pain was evaluated at least 2 hours after arising in the morning. The FIHOA score was used as a quantitative measure of functional disability in the target hand. Patients reported the severity of their symptoms by answering a set of 10 questions, each of which was scored on a numerical scale of 0–3, where 0 = movements possible without difficulty, 1 = movements possible with slight difficulty, 2 = movements possible but with great difficulty, and 3 = movements impossible. Severity scores ranged from 0 to 30 points, with 30 representing the worst possible score.

A set of secondary outcomes was also assessed. Changes in grip strength in both hands were assessed using a Jamar dynamometer (21). The patients sat upright in a straight-backed chair with back support, in a position that allowed the hips and knees to lie at right angles and the elbow to be flexed to 90° between pronation and supination. They were required to grip the dynamometer handle and squeeze as hard as possible according to their individual pain limits. The right hand grip was measured first, then the left; this procedure was performed 3 times. The mean value of these 3 measurements was recorded. The duration of morning stiffness and the average weekly consumption of acetaminophen (500-mg tablets) were also recorded. The investigator's global impression of efficacy was graded on a 4-point ordinal scale (marked improvement, slight improvement, doubtful improvement, or no improvement in the patient's clinical condition). The presence of erosive hand OA and rhizarthrosis on baseline radiographs was assessed by an experienced osteoarticular radiologist (FK) who was blinded with regard to the treatment allocation. Erosive OA was operationally defined by the presence of nonuniform loss of joint space related to central (not marginal) erosions combined with osteophytes, producing a "seagull" appearance in the PIP and DIP joints.

Safety parameters. The patients' spontaneous reporting of adverse events (AEs) to the investigator was used to assess the tolerability profile of the study treatment. The potential relationship of the AE to study medication administered during the course of the trial was evaluated by the investigator. The patient's assessment of overall tolerability was determined at each visit using a 4-point ordinal verbal scale (excellent, good, fair, or poor).

Statistical analysis. We estimated that a total of 152 patients (76 patients in each group) would be required to demonstrate a 10-mm difference in improvement in the patient's assessment of global spontaneous hand pain (using a 0–100-mm VAS) between the 2 groups, with an SD of 20 mm, a power of 80%, an error alpha value of 5%, and a dropout rate of 15% (22).

The main analysis for efficacy and safety was an intent-to-treat analysis. Missing followup assessments were replaced using the last observation carried forward (LOCF) method. Alternative techniques of imputing missing followup assessments were performed to test the robustness of this assumption. We performed a sensitivity analysis using linear interpolation (mixed regression model) for missing followup assessments. We further performed a per-protocol completer analysis including only patients who completed the planned treatment. Overall, sensitivity analyses yielded qualitatively very similar results to those from the LOCF analysis, suggesting that results were not driven by selective dropouts or differential missing data.

Standard descriptive statistics were used to describe the demographic data and baseline disease characteristics. We used unpaired *t*-tests for normally distributed variables, Wilcoxon's rank sum tests for continuous non-normally distributed variables, and chi-square tests for dichotomous variables to verify homogeneity between treatment groups.

The significance of intergroup differences in score changes at 6 months was analyzed by means of Student's *t*-test or Wilcoxon's rank sum test, where appropriate. The Cochran-Mantel-Haenszel test was used to compare the investigator's global impression of efficacy and tolerability, and chi-square test was use to analyze the frequency of AEs. Further, to test whether the longitudinal evolution in the primary or secondary outcomes differed between the two treatment groups during the 6-month trial period, we used an analysis of covariance model, including baseline levels as covariates. We also explored whether the main results were modified (effect modification) by clinical parameters, such as the presence of erosive OA or the presence of rhizarthrosis. All statistical tests were 2-sided, and *P* values less than or equal to 0.05 were considered significant. The statistical analysis was performed using SAS Software (release 8.2) on a Windows XP operating system, as well as Stata MP version 11.1 for Windows (StataCorp).

RESULTS

Clinical assessment. Of the 562 patients who were screened, 162 met the inclusion criteria. These patients were enrolled in the clinical trial and included in the intent-to-treat analysis (80 patients in the CS group and 82 patients in the placebo group). The remaining 400 patients could not be randomized be-

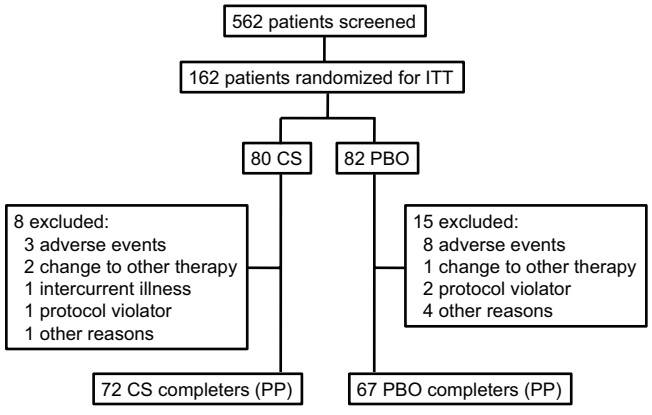

Figure 1. Flow chart showing the distribution of the study patients. Of the 562 osteoarthritis (OA) patients who were screened, 162 met the inclusion criteria and were randomized to 1 of the 2 study treatment arms (intent to treat [ITT]): chondroitin sulfate (CS; 800 mg/day) or placebo (PBO). The number and main reasons for study discontinuations are listed. The study was completed by 72 and 67 patients in the CS and placebo groups, respectively (per protocol [PP]).

Table 1. Baseline demographic and clinical characteristics of the patients with OA of the hand, by treatment group*

	CS (n = 80)	Placebo (n = 82)
Age, mean ± SD years	63.9 ± 8.5	63.0 ± 7.2
Sex, no. male/female	22/58	20/62
BMI, mean ± SD kg/m^2	26.7 ± 4.5	25.0 ± 3.9
Handedness		
No. with dominant left hand/right hand	25/55	26/56
% with dominant right hand	69	68
No. with target left hand/right hand	23/57	27/55
Symptom duration, mean ± SD years		
Left hand	6.9 ± 6.3	6.2 ± 5.3
Right hand	7.1 ± 6.1	6.7 ± 5.7
No. of painful flares in 12 months, mean ± SD	35.2 ± 80.0	30.0 ± 70.3
No. of PIP nodal joints, mean ± SD		
Left hand	1.0 ± 1.5	0.9 ± 1.2
Right hand	1.2 ± 1.6	1.0 ± 1.2
No. of DIP nodal joints, mean ± SD		
Left hand	2.1 ± 1.4	2.0 ± 1.4
Right hand	2.4 ± 1.3	2.1 ± 1.4
Patient's assessment of global hand pain, mean ± SD mm		
Left hand	43.8 ± 21.0	42.4 ± 21.4
Right hand	48.7 ± 19.3	45.9 ± 19.2
Target hand	54.9 ± 14.2	53.6 ± 14.2
FIHOA score, mean ± SD	11.0 ± 4.1	10.3 ± 3.8
No. of fingers with osteophytes on PIP joints, mean ± SD		
Left hand	1.9 ± 1.6	1.9 ± 1.5
Right hand	2.3 ± 1.5	1.9 ± 1.5
No. of fingers with osteophytes on DIP joints, mean ± SD		
Left hand	2.9 ± 1.3	3.0 ± 1.2
Right hand	3.1 ± 1.3	3.1 ± 1.1
No. (%) of patients with erosive hand OA	26 (33)	35 (43)
No. (%) of patients with rhizarthrosis	37 (47)	43 (53)

* The target hand was defined as the patient's more symptomatic hand or, when both hands were equally painful, the patient's dominant hand. The patient's assessment of global spontaneous hand pain intensity was determined with the use of a 0–100-mm visual analog scale. Only the body mass index (BMI) was significantly different between the group who took chondroitin sulfate (CS; 800 mg/day) and the group who took placebo ($P = 0.01$). OA = osteoarthritis; PIP = proximal interphalangeal; DIP = distal interphalangeal; FIHOA = Functional Index for Hand OA (range 0–30).

cause their pain and FIHOA scores were below those required for study inclusion, they took CS or other drugs that were not allowed, or they did not fulfill the ACR classification criteria for OA of the hand. A total of 139 patients completed the 6-month treatment per protocol (Figure 1).

Table 2. Changes in global pain and FIHOA scores between baseline and 6 months, by treatment group*

	CS (n = 80)			Placebo (n = 82)			Difference in change scores between groups
	Enrollment, visit 0	Last visit, month 6	Change	Enrollment, visit 0	Last visit, month 6	Change	
Patient's assessment of global hand pain, mm							
Mean ± SD	54.9 ± 14.2	34.9 ± 25.3	−20 ± 26	53.6 ± 14.2	42.3 ± 24.9	−11.3 ± 24.0	−8.7†
Range	40–90	0–100	−50–83	40–100	0–90	−31–81	
FIHOA score							
Mean ± SD	11.0 ± 4.1	8.2 ± 5.9	−2.9 ± 5.3	10.3 ± 3.8	9.6 ± 5.6	−0.7 ± 4.8	−2.14‡
Range	6–23	0–22	−10–16	6–26	0–23	−14–13	

* The patient's assessment of global spontaneous hand pain intensity was determined with the use of a 0–100-mm visual analog scale. FIHOA = Functional Index for Hand Osteoarthritis (range 0–30); CS = chondroitin sulfate (800 mg/day).
† $P = 0.016$ by Wilcoxon's rank sum test.
‡ $P = 0.008$ by Student's t-test.

Baseline characteristics of the 162 study patients, including the percentage of patients under treatment during the previous 3 months, the duration of symptoms in both hands, the occurrence of OA flares during the previous 12 months, and the mean numbers of fingers with nodal PIP and DIP joints or PIP/DIP osteophytes, were balanced between the two treatment groups. These data are summarized in Table 1. Furthermore, the patient's assessment of global hand pain intensity as measured by VAS and hand function as assessed by the FIHOA score were also balanced between the treatment groups at baseline (Table 2). A total of 61 patients had signs of erosive hand OA at baseline: 33% in the CS group and 43% in the placebo group ($P = 0.18$). Rhizarthrosis was present in 80 patients, 47% taking CS and 53% taking placebo ($P = 0.43$). The occurrence of AEs was the main reason for study withdrawal: 3 patients in the CS group (3.8%) and 8 patients in the placebo group (9.8%).

Improvement in the patient's assessment of global hand pain was significantly more pronounced in the CS group than in the placebo group (mean ± SD 20 ± 26 versus 11.3 ± 24.0 mm; between-group difference in the amount of change –8.7 mm [$P = 0.016$]). The intergroup difference in absolute global pain levels at 6 months was –7.4 mm in favor of CS (34.9 ± 25.3 versus 42.3 ± 24.9 mm in the placebo group). The decrease in the FIHOA score demonstrated a similar pattern (mean ± SD −2.9 ± 5.3 in the CS group and −0.7 ± 4.8 in the placebo group; between-group difference in the amount of change −2.14 [$P = 0.008$]). The intergroup difference in absolute levels of FIHOA at 6 months was −1.4 in favor of CS (8.2 ± 5.9 versus 9.6 ± 5.6 in the placebo group). The relative benefit of CS on the patient's assessment of global spontaneous hand pain scores and on the FIHOA scores started to become evident only after 3 months of treatment (Figure 2 and Table 2).

The presence of erosive OA was significantly associated with a higher FIHOA score at baseline (11.79 versus 9.98; $P = 0.005$), but not with global pain intensity (54.5 versus 53.8; $P = 0.75$). Rhizarthrosis was also associated with a higher FIHOA score at baseline (11.3 versus 10.1; $P = 0.059$), but not with global pain intensity (53.0 versus 55.1; $P = 0.35$). However, neither erosive OA nor rhizarthrosis influenced the effect of therapy (no effect modification) on the global hand pain and on function, nor were the results substantially changed when adjusted for radiographic evidence of erosive OA or rhizarthrosis in a multivariate analysis.

The duration of morning stiffness was slightly but

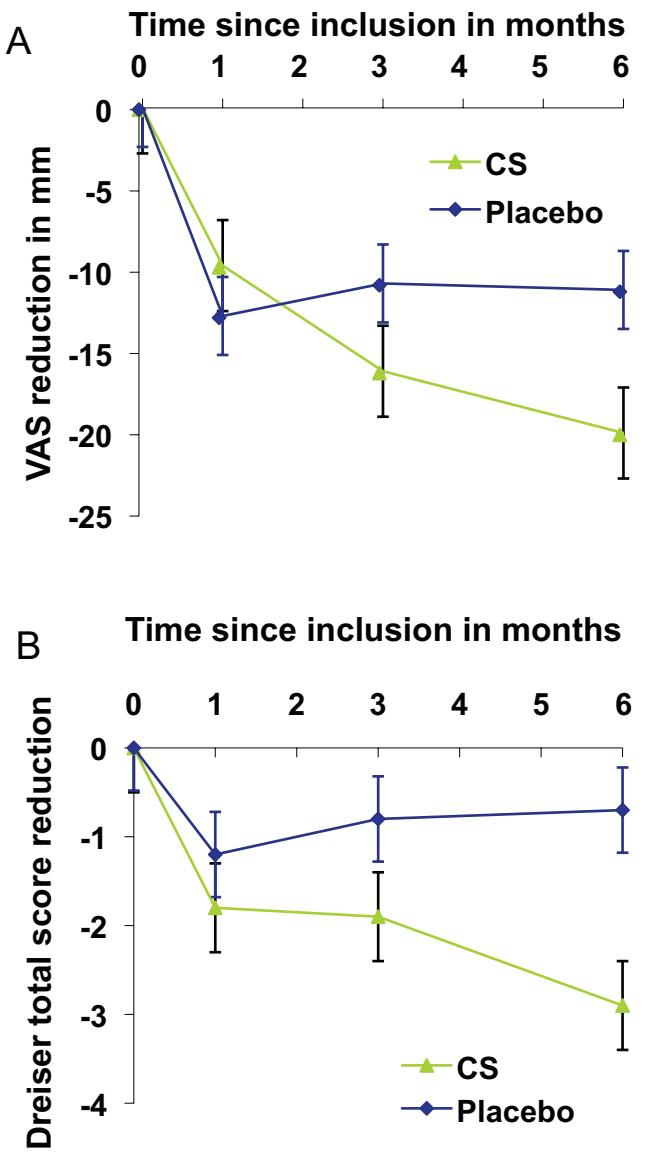

Figure 2. Evolution of the patient's assessment of global spontaneous hand pain and Functional Index for Hand OA (FIHOA) scores in patients treated with chondroitin sulfate (CS) or placebo. Scores for the patient's global assessment of hand pain, as determined with a visual analog scale (VAS; 0–100 mm) (**A**) and for the FIHOA (0–30 scale) (**B**) were determined at baseline and at 1, 3, and 6 months in 80 patients in the CS group and 82 patients in the placebo group. See Table 2 for explanations of statistical comparisons.

significantly reduced at the last visit in patients treated with CS as compared to those treated with placebo (mean ± SD −4.8 ± 22.4 versus 0.3 ± 12.0 minutes; difference of changes −5.1 minutes [$P = 0.031$]). At the final visit, the mean grip strength had improved

Table 3. Changes in secondary outcomes between baseline and 6 months, by treatment group*

	CS (n = 80)			Placebo (n = 82)		
	Enrollment, visit 0	Last visit, month 6	Change	Enrollment, visit 0	Last visit, month 6	Change
Grip strength, kg/cm^2						
Mean ± SD	24.0 ± 9.1	26.5 ± 10.8	2.5 ± 6.6	25.0 ± 10.5	25.6 ± 9.9	0.6 ± 5.8
Range	9–50	5–56	−8–32	4–58	3–55	−32–18
Duration of AM stiffness, minutes						
Mean ± SD	16.2 ± 19.8	11.4 ± 16.6	−4.8 ± 22.4†	11.7 ± 12.9	12.0 ± 12.7	0.3 ± 12.0
Range	0–120	0–60	−60–105	0–60	0–60	−30–35

* CS = chondroitin sulfate (800 mg/day).
† $P = 0.031$ versus placebo, by Wilcoxon's rank sum test.

in the CS group (mean ± SD 2.5 ± 6.6 kg/cm^2 versus 0.6 ± 5.8 kg/cm^2 in the placebo group; effect size 1.9 kg/cm^2 [$P = 0.132$]) (Table 3).

No statistically significant differences in acetaminophen consumption as pain rescue medication (mean ± SD 1.9 ± 2.8 500-mg tablets/week in the CS group and 2.0 ± 4.2 500-mg tablets/week in the placebo group) or in compliance with the study treatment (good/excellent in 88% of the CS group and in 97% of the placebo group) were observed between the two treatment groups. The investigator's global impression of treatment efficacy progressively increased over time in patients receiving CS, whereas it remained practically unchanged in patients receiving placebo. At the 6-month visit, the number of patients with slight or marked improvement was significantly higher in the CS group than in the placebo group (44% versus 33%; $P = 0.043$).

Findings of the safety analysis. Overall, 138 AEs were reported by 68 patients throughout the 6-month trial (67 AEs in 34 patients receiving CS [42.5%] and 71 AEs in 34 patients receiving placebo [41.5%]). Most of these AEs were classified as mild or moderate in intensity (80.6% and 87.3%, respectively). A total of 10 serious AEs (SAEs) were reported by 4 patients (2 SAEs in 2 patients in the CS group [2.5%] and 8 SAEs in 2 patients in the placebo group [2.4%]). Only 1 SAE (abdominal pain) occurring in a patient treated with placebo was rated by the investigator as being potentially related to the study medication. The remaining 9 SAEs were considered to be unrelated to the study medication.

The distribution of adverse drug reactions (ADRs) is presented in Table 4. No serious ADRs occurred in any of the patients included in this study. Gastrointestinal disorders, infections and infestations, nervous system disorders, and musculoskeletal disorders were the AEs/ADRs most frequently reported. These were almost equally distributed in the two treatment arms.

Of the 3 patients in the CS group who withdrew from the study because of AEs/SAEs, 1 experienced a myocardial infarction, which was rated as being unrelated to the study treatment, and 2 complained of benign gastrointestinal problems, which were considered to be possibly/probably drug related. Of the 8 patients in the placebo group who withdrew from the study because of AEs/SAEs, 1 experienced anemia, 1 had a nonserious central nervous system condition (both of these were regarded as being unrelated to the study treatment), and the remaining 6 patients had AEs of the gastrointestinal

Table 4. Adverse drug reactions by body system and treatment group*

	CS (n = 67)	Placebo (n = 71)
No. (%) of patients with adverse drug reactions	13 (19.4)	19 (26.8)
GI system, no. of events		
Total GI disorders	12	14
Diarrhea	4	4
Dyspepsia	3	2
Nausea	2	2
Abdominal pain	2	1
Constipation	1	1
Abdominal distension	0	1
Upper abdominal pain	0	1
Flatulence	0	1
Hyperchlorhydria	0	1
Musculoskeletal system		
Total musculoskeletal disorders	0	1
Pain in extremity	0	1
Nervous system		
Total nervous system disorders	1	3
Dizziness	0	1
Headache	0	1
Neuralgia	0	1
Paresthesia	1	0
Skin and SC system		
Total skin and SC tissue disorders	0	1
Skin rash	0	1

* CS = chondroitin sulfate (800 mg/day); GI = gastrointestinal; SC = subcutaneous.

system, including 1 case of appendicitis and 1 occurrence of changes in liver function (both of these were regarded as being unrelated to the study treatment). At the final visit, the investigator's global impression of tolerability was graded as good or excellent in the majority of cases (96.3% in CS-treated patients and 90.8% in placebo-treated patients).

DISCUSSION

The results of this clinical trial demonstrated that 6 months of treatment with CS is significantly superior to placebo with regard to improvements in global hand pain and hand function in patients with symptomatic OA of the hand. In addition, CS was also associated with a significant decrease in the duration of morning stiffness, but had no statistically significant effect on grip strength or on the consumption of acetaminophen for pain. The benefits of CS were not influenced by the presence of rhizarthrosis or erosive OA. Finally, as reported in previous studies of CS therapy, we did not observe any safety problems with CS.

Despite the frequency of hand OA, only a limited number of studies have examined the effect of pharmacologic therapies in the management of hand OA. Three short-term placebo-controlled clinical trials have examined the efficacy of NSAIDs in patients with hand OA (13,23,24) and demonstrated significant efficacy of this therapeutic class on pain. In the largest of these trials (23), the difference in the change in global hand pain (assessed by VAS at 4 weeks) was between 8.7 mm and 10.7 mm, depending on the NSAID dose. The effect of NSAIDs on the FIHOA score was assessed in only 1 trial, which evaluated ibuprofen; there was a difference of −2.76 units in the change in FIHOA scores at 2 weeks as compared to placebo.

While direct comparisons of the efficacy of CS versus NSAIDs are not possible in the absence of head-to-head evaluations, the difference in change scores for hand pain and function in relation to NSAID treatment appears to be of similar magnitude as observed with CS in the present study. Although the difference in change scores for global hand pain was significantly more pronounced in patients treated with CS as compared to placebo, the magnitude of the difference was relatively modest. Thus, whether this statistically significant difference has a clinical impact remains to be demonstrated. The presence of a positive effect on the evolution of the FIHOA scores at 6 months, however, is indicative of a positive clinical effect of CS in this study population.

The results of RCTs suggest that NSAIDs are associated with an increased occurrence of gastrointestinal AEs, even in short-term studies (13,24). In addition, the increased occurrence of cardiovascular side effects associated with long-term use of NSAID may have an important effect in patients with hand OA. Indeed, epidemiologic studies have demonstrated that hand OA is associated with an increased body mass index (25), carotid plaque, and coronary calcifications in women, suggesting that hand OA could be a metabolic disease (26). Symmetric OA of the DIP joints is associated with increased mortality rates in women (relative risk 1.23 [95% confidence interval (95% CI) 1.01–1.51]), and OA of any finger joint is predictive of death from cardiovascular causes in men (relative risk 1.42 [95% CI 1.05–1.92]) (4). Thus, the long-term use of NSAIDs (both selective and nonselective cyclooxygenase 2 inhibitors) may further increase the risk of cardiovascular events in a relatively high-risk population and should be used with caution.

Acetaminophen is generally considered to be a safe alternative to NSAIDs in the management of OA (11). However, in a short-term RCT, acetaminophen appeared to be less effective than oral NSAIDs on the duration of morning stiffness in patients with hand OA (27). In addition, regular use of acetaminophen may increase blood pressure, particularly in patients with increased cardiovascular risk (28), thus raising concerns about the long-term use of acetaminophen in elderly patients with OA. Overall, the main advantage of analgesics or NSAIDs in OA is prompt symptomatic relief, while the long-term use of these agents carries a substantial risk of drug-related adverse reactions. In contrast, the beneficial effects of CS appear to take several months to develop, but with hardly any side effects, and this could help to reduce the need for long-term NSAID therapy in patients with hand OA.

Alternative measures for the treatment of hand OA are topical agents, such as topical NSAIDs, which in short-term RCTs, appear to be safe but only modestly effective. Indeed, diclofenac gel was significantly better than placebo gel on improvement in global hand pain at weeks 4 and 6, but this effect was lost at the end of the study, with a mean difference of 5.9 mm in global pain scores between placebo and diclofenac gels ($P = 0.06$) (14). Application of capsaicin creams has also demonstrated an effect on self-assessed pain and tenderness as compared to a placebo cream (15). Taken together, the results of these studies suggest that topical therapies may represent a safe, but only modestly effective, alternative for the management of hand OA. However, the

need for frequent applications may limit their use in the management of chronic conditions.

In the present trial, the effects of CS on hand function (FIHOA score) seemed more pronounced than the effects on global assessment of hand pain. This finding is unexpected, since the FIHOA score was previously reported to be less sensitive to change than the global hand pain assessment (29). However, other investigators have found a more pronounced effect of therapy on hand function than on hand pain (14), and it is plausible that symptomatic treatment may have a greater effect on hand function and for a longer period of time than on pain control. A potential chondroprotective effect of CS has been demonstrated in 2 RCTs in patients with knee OA (30,31). However, due to the short duration of the present trial, it is unlikely that the positive effect of CS on hand function is directly related to its potential protective effects on structural damage.

The structural effects of CS on hand OA has been evaluated previously in a clinical study that pooled data from treatment with either CS or chondroitin polysulfate and confirmed a modest slowing of OA progression in affected joints (18). Another small study suggested that the combination of CS and naproxen was superior to naproxen alone on the progression of joint erosions (32). The primary objective of this clinical trial was to assess the symptomatic effects of CS in patients with hand OA. We measured surrogate markers of cartilage degradation, such as serum cartilage oligomeric matrix protein, serum cartilage glycoprotein 39, and urine C-terminal crosslinking telopeptide of type II collagen, at baseline and at the end of study. After 6 months, the levels of all these biomarkers were not different in CS-treated versus placebo-treated patients (data not shown). This result can be explained by the fact that these biomarkers are not sensitive for detecting modest effects on articular cartilage, particularly if OA is restricted to the hands. We did not collect data regarding the presence of OA in other joints, which limits the interpretation of the results. Further studies using more sensitive biomarkers and imaging techniques may provide informative results on the potential chondroprotective effects of CS in hand OA.

Some limitations of our study need to be discussed. First, while this study has sufficient power to detect meaningful changes in the primary outcomes, the sample size may be inadequate to demonstrate change in the secondary outcomes. Furthermore, the study may have insufficient power to detect effect modification in specific subgroups, such as different types of hand OA. Finally, we restricted study inclusion to patients presenting with severe symptomatic hand OA, which limits the generalization of our results to patients with substantial symptoms from their hand OA. The effect of CS on OA hand pain can be considered moderate, but it was sufficient to result in significantly more patients being assessed by their physician as having improved. Furthermore, currently available therapeutic alternatives, such as NSAIDs, display similar effect sizes with significantly more long-term toxicities.

In conclusion, this study demonstrates that CS is effective and safe in the treatment of patients with hand OA. CS represents an interesting therapeutic alternative for the management of this frequent condition.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gabay had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gabay, Medinger-Sadowski.
Acquisition of data. Medinger-Sadowski, Gascon, Kolo.
Analysis and interpretation of data. Gabay, Finckh.

ROLE OF THE STUDY SPONSOR

This randomized controlled trial was initiated by the investigators, who designed the study, performed the trial in their own center, independently transcribed the study outcomes from the Case Report Form, analyzed the data, and wrote the manuscript. The Institut Biochimique SA (IBSA) had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by the IBSA.

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