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Long-Term Effects of Chondroitins 4 and 6 Sulfate on Knee Osteoarthritis

The Study on Osteoarthritis Progression Prevention, a Two-Year, Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. **To assess the long-term effects of chondroitins 4 and 6 sulfate (CS) on the radiographic progression of, and symptom changes associated with, knee osteoarthritis (OA).**

Methods. **We performed an international, randomized, double-blind, placebo-controlled trial in which 622 patients with knee OA were randomly assigned to receive either 800 mg CS (n = 309 patients) or placebo (n = 313 patients) once daily for 2 years. Radiographs of the target knee, using the Lyon schuss view, were obtained at the time of enrollment and at 12, 18, and 24 months. The minimum joint space width (JSW) of the medial compartment of the tibiofemoral joint was assessed by digital image analysis. The primary outcome was the loss in minimum JSW over 2 years.**

Results. **The intent-to-treat analysis demonstrated a significant reduction ($P < 0.0001$) in minimum JSW loss in the CS group (mean ± SEM −0.07 ± 0.03 mm) as compared with the placebo group (−0.31 ± 0.04 mm). The percentage of patients with radiographic progression ≥0.25 mm was significantly reduced in the CS group compared with the placebo group (28% versus 41% [$P < 0.0005$]; relative risk reduction 33% [95% confidence interval 16–46%]). The number of patients needed to treat was 8 (95% confidence interval 5–17). Pain improved significantly faster in the CS group than in the placebo group ($P < 0.01$). There were no differences in safety between groups.**

Conclusion. **The long-term combined structure-modifying and symptom-modifying effects of CS suggest that it could be a disease-modifying agent in patients with knee OA.**

Osteoarthritis (OA) is the most prevalent musculoskeletal condition, an important cause of disability, and a major public health problem (1,2). Current options for rapidly acting drug therapy usually include analgesics or nonsteroidal antiinflammatory drugs (NSAIDs) (3,4). Slow-acting drugs for the treatment of OA have been classified as symptom-modifying and disease-modifying; the latter classification applies to drugs that can retard or stop joint structure degradation and thus slow progression of the disease (5–7). The main

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evaluation criterion for disease-modifying drugs is the prospective evaluation of radiographic changes by analysis of the minimum joint space width (JSW) (7). Structure-modifying effects have been suggested in randomized clinical trials with diacerein (8) for hip OA and with glucosamine sulfate (9,10) and chondroitins 4 and 6 sulfate (CS) (11) for knee OA.

The Study on Osteoarthritis Progression Prevention (STOPP) was conducted to establish whether CS could both improve symptoms and delay joint structure degradation over 2 years in patients with knee OA.

PATIENTS AND METHODS

Study design and selection of patients. The study group comprised patients from France, Belgium, Switzerland, Austria, and the US who were enrolled between February 2000 and July 2002 (see Appendix A for a list of participating physicians and study centers). The main inclusion criteria were outpatient status, age between 45 years and 80 years, and primary knee OA of the medial tibiofemoral compartment diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology (12). The symptomatic knee (with a pain score of at least 30 mm on a 0–100-mm visual analog scale [VAS] for at least 3 months before enrollment and minimum JSW of at least 1 mm) was defined as the target knee. If both knees were symptomatic, the knee with the narrowest JSW was selected. If both knees had the same JSW, the more symptomatic knee was chosen.

The major exclusion criteria were grade 4 radiographic OA according to the Kellgren/Lawrence grading system (7,13); isolated lateral tibiofemoral OA; isolated patellofemoral OA; a history of surgery in the target knee; traumatic lesions in the target knee; a history or the active presence of other rheumatic diseases that could be responsible for secondary OA, including calcium pyrophosphate deposition disease (6,7); significant hip OA; a history of hip surgery; substantial abnormalities in hematologic, hepatic, renal, cardiac, lung, or neurologic function; infectious disease; major surgery foreseen during the 2-year study period; intraarticular injection in the target knee in the 3 months preceding enrollment; treatment with symptomatic slow-acting or disease-modifying OA drugs in the 3 months preceding enrollment; or corticosteroid administration in the month preceding enrollment. Physical therapy was not allowed during the study period.

The study was approved by the ethics committee of the Cochin University Hospital, Paris, France, and the ethics committees of all other participating study centers. All patients gave their written informed consent to participate.

Treatment assignment. Patients were randomly assigned to receive either an 800-mg sachet of CS (Genévrier Laboratories, Sophia Antipolis, France, and IBSA, Pambio Noranco, Switzerland) or an identical sachet of placebo daily, taken every evening with a glass of water, for 2 years. CS and placebo were packed in anonymous sachets of identical appearance, containing oral gel with the same aspect, odor, and flavor; both CS and placebo sachets contained sodium benzoate and potassium sorbate. CS contained highly purified chondroitins 4 and 6 sulfate of bovine origin in a concentration not less than 95% (European patents EP1582214 and EP1705192); this product has been approved as a prescription treatment for OA at a daily dose of 800 mg in many European countries. The prescription drug has been certified for the absence of viral or other infectious diseases risks.

For rescue analgesia, patients were allowed to take acetaminophen in 500-mg tablets (maximum dosage 4 gm/day); NSAIDs were allowed in cases of acute pain and were quantified as grams of ibuprofen equivalent. Use of rescue medication was recorded by the patients in a diary, and appropriate washout periods (24 hours for acetaminophen and 5 days for NSAIDs; i.e., at least 5 half-lives of the selected medication) were allowed before symptom assessment. Compliance with the study treatment was established by asking the patients about missed doses and by counting unused study drug sachets and acetaminophen tablets. Arthrocentesis was permitted for persistent significant hydrarthrosis, but the intraarticular injection of corticosteroids was forbidden. No other cointerventions for OA were allowed. All other medications used by the patients, including hormone replacement therapy, were recorded.

The randomization list was generated by computer in blocks of 4, and patients received their randomization number in chronological order. The principal investigator (AK) was provided with individual envelopes, each containing patient codes, thus concealing treatment assignment. At the end of the study, after the data bank was completed, the randomization list was provided to the statistician (FDV), who remained blinded to treatment assignments.

Outcome measures. The primary outcome criterion for joint structural changes, defined a priori by expert consensus, was modification in the minimum JSW of the medial compartment of the target tibiofemoral joint. The medial tibiofemoral joint space, rather than the lateral space, is preferred in clinical trials because this is the area that is subjected to the most OA cartilage loss and for which outcome measures are better validated (6).

Posteroanterior Lyon schuss radiographs of the target knee were obtained at the time of enrollment and at 12, 18, and 24 months, using a standardized technique (14). Briefly, the degree of flexion was set as a result of positioning the patient with the tips of the great toes, knees, thighs, and pelvis coplanar and in contact with the examination table; this position yields a 20–30° flexion of the knee, depending on each patient's length of tibia and feet, which remains constant in serial radiographs of a given subject, leading to high reproducibility of joint positioning. Because patellas were in contact with the table, less change in the image size of the knee was observed. The source-to-film distance was 110 cm. The central x-ray beam was directed at the center of the joint, in the space between the tibial spines and the femoral notch. Fluoroscopy was used in all study centers in order to obtain good alignment of the anterior and posterior margins of the medial tibial plateau (14). In all radiography departments, the radiographs were obtained by specifically trained radiology technicians. All radiographs were digitized. All radiographs from all centers were blinded with regard to the patient's name, treatment assignment, and time sequence; the principal investigator (AK) was provided with the radiography list at the time of randomization.

First, all radiographs were measured by a single experienced reader who was unaware of the treatment assignment and time sequence of the radiographs. The statistical analysis of this first radiographic assessment demonstrated the efficacy of CS as compared with placebo (15).

In order to assess whether these findings were robust, the radiographs were then blinded and randomized by Pr. H. Landmann (Dresden, Germany), an assessor independent of the investigators and the pharmaceutical company. All radiographs were measured by a second independent experienced reader who was unaware of the treatment assignment and time sequence of the radiographs as well as the first measurement results. This second series of radiographic measurements, which are described in the present report, showed similar results, with a linear correlation (r^2) of 0.9886 between the 2 series of measurements.

The minimum JSW of the medial compartment of the tibiofemoral joint was measured using validated digitized image analysis software (Explora Nova Knee JSWa version v1.70f; La Rochelle, France). The procedure for defining landmarks was as follows: after calibration and contrast adjustment, the observer moved 2 vertical lines in contact with the convexity of the medial and lateral femoral condyle margins. Two lines were automatically generated in every compartment (the first at 10 mm from the condyle line, the second at 15 mm from the preceding one). In the area delimited by these 2 lines, the operator detected tibial and femoral bone edges. The diameter of the smallest circle included in this area was automatically measured in the internal compartment and corresponds to the minimum JSW (16).

Prior to the other analyses, reproducibility of the measurement of the minimum JSW was assessed. A first evaluation was performed by twice measuring 100 radiographs from STOPP. These radiographs were randomly determined and blinded for measurement. The intraclass correlation coefficient between repeated measurements of the same film was 0.99, and the coefficient of variation was 1.2%. The mean ± SD difference between the 2 measurements was 0.01 ± 0.12 mm (range −0.33 to +0.39); the smallest detectable difference obtained was 0.25. Thus, patients with radiographic progression were defined, before the study code was broken, as those with a decrease in the minimum JSW of at least 0.25 mm. A confirmatory evaluation of reproducibility was performed, measuring another set of 30 randomly determined and blinded radiographs. The mean ± SD difference between the 2 measurements was 0.01 ± 0.15 mm (range −0.34 to +0.30). Furthermore, the patients with clinically relevant radiographic progression according to the results of previous studies were defined by expert consensus, before the study code was broken, as those with a decrease in the minimum JSW of at least 0.50 mm (17).

Clinical assessments of the patients were performed 1 month before enrollment, at the time of enrollment, 1 month and 3 months after enrollment, and every 3 months thereafter for up to 2 years. Symptoms of OA were assessed by the patient's estimate of pain during the previous 48 hours, using a 100-mm VAS and by the Western Ontario and McMaster Universities OA Index (WOMAC) (18). The VAS version of the WOMAC index was used, with the patient answering each question using a 100-mm VAS. The WOMAC score was analyzed using normalized 100-mm scales. The secondary outcome criteria, defined a priori by expert consensus, included target knee pain (VAS), WOMAC score (total and subscales), global efficacy (VAS) assessed independently by the patient and the doctor, cumulative consumption of acetaminophen, and cumulative consumption of NSAIDs. The withdrawal rates and their causes were compared between groups. Tolerability was assessed on a 4-point ordinal scale (very good, good, fair, and poor). Any adverse event and abnormal results of routine laboratory tests were reported.

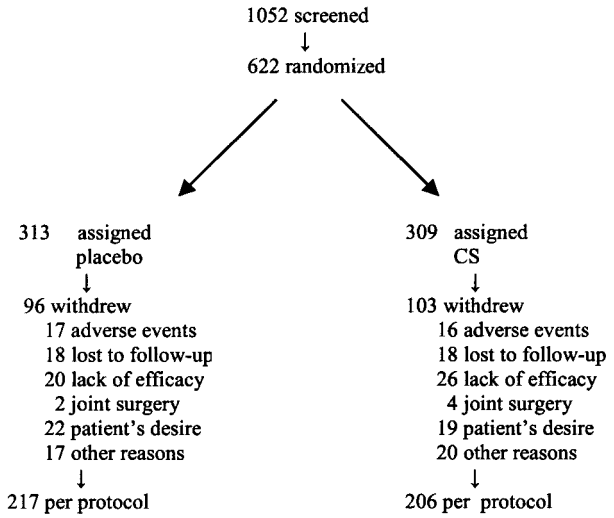

Figure 1. Trial profile. CS = chondroitin sulfate.

Statistical analysis. We calculated the sample size of 600 patients on the basis of the recommendations available at the time of study planning, with the hypotheses that there would be 0.16 mm of difference in joint space narrowing in 2 years between the 2 groups, with an SD of 0.6 mm, a power of 80%, an alpha risk of 5%, and a 30% dropout rate (5). Intent-to-treat (ITT) analyses were performed for all randomized patients, using the last observation carried forward approach. Per-protocol completer analyses were performed on patients who completed the 2-year observation period.

Characteristics at the time of inclusion were assessed using the chi-square test or Fisher's exact test for qualitative variables, the chi-square linear trend test for semiquantitative variables with few classes, and nonparametric tests for quantitative variables. In case of a difference between the 2 treatment groups, an additional adjusted analysis was planned. Analysis of variance for repeated measurements also had to be performed on the values of the variables or on the ranks, according to normality or the absence of normality.

The variation in the minimum JSW was planned to be analyzed with Student's *t*-test or a nonparametric test according to the normality or absence of normality of the distribution; the effect of treatment and its 95% confidence interval (95% CI) had to be estimated using the Hodges-Lehmann estimator, in case of non-normality of the distribution.

The percentage of patients with radiographic progression was compared between groups, using the chi-square test. Furthermore, the sensitivity of this analysis was assessed using

Table 1. Demographic and baseline clinical characteristics of all patients*

Characteristic	All randomized patients		Patients assessed for 2 years	
	Placebo (n = 313)	CS (n = 309)	Placebo (n = 217)	CS (n = 206)
Women, no. (%)	209 (67)	216 (70)	143 (66)	145 (70)
Age, years	61.8 ± 0.5	62.9 ± 0.5	61.6 ± 0.5	62.8 ± 0.6
Body mass index, kg/m^2				
Men	28.3 ± 0.4	28.3 ± 0.4	28.5 ± 0.5	28.2 ± 0.5
Women	29.3 ± 0.4	28.6 ± 0.4	29.2 ± 0.5	28.3 ± 0.4
Duration of knee OA, years				
Left knee	6.5 ± 0.4	6.1 ± 0.3	6.4 ± 0.4	6.0 ± 0.4
Right knee	6.3 ± 0.4	6.6 ± 0.4	6.3 ± 0.4	6.5 ± 0.4
K/L grade, %†				
1	19.7	17.4	19.3	19.4
2	21.6	26.2	19.3	25.7
3	58.7	56.4	60.4	54.9
Minimum JSW, mm	3.81 ± 0.07	3.73 ± 0.08	3.73 ± 0.08	3.72 ± 0.09
Pain score, 100-mm VAS	57.3 ± 1.0	57.2 ± 0.9	57.3 ± 1.2	55.4 ± 1.1
WOMAC score, mm‡				
Total	41.6 ± 1.2	40.5 ± 1.2	41.1 ± 1.5	37.6 ± 1.4
Pain	40.5 ± 1.2	40.0 ± 1.2	40.0 ± 1.4	37.7 ± 1.4
Function	39.0 ± 1.2	39.2 ± 1.3	39.3 ± 1.5	35.6 ± 1.5
Stiffness	43.5 ± 1.5	42.3 ± 1.5	43.9 ± 1.8	39.4 ± 1.8

* Except where indicated otherwise, values are the mean ± SEM. The duration of knee osteoarthritis (OA) was based on patient history. There were no statistically significant differences between groups. CS = chondroitin sulfate; OA = osteoarthritis; JSW = joint space width.
† The Kellgren/Lawrence (K/L) system grades OA on joint radiographs as 0 = none, 1 = doubtful, 2 = mild, 3 = moderate, and 4 = severe, based on the assumed sequential appearance of osteophytes, joint space loss, subchondral sclerosis, and cyst formation.
‡ The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score represents the sum of the visual analog scale (VAS) scores for each item, using normalized 100-mm scales.

other threshold values for the decrease in the minimum JSW, from 0.05 mm to 0.7 mm, per 0.05-mm step.

Secondary outcome measures for the evaluation of symptom modification, including changes in the VAS pain score, the total WOMAC score, and the WOMAC subscale scores, were assessed using repeated-measures analyses of variance.

The cumulative consumption of rescue medications was compared between the 2 study groups using Wilcoxon's test. Adverse events and dropout rates were analyzed using the chi-square or Fisher's exact test (2-tailed), as appropriate. All statistical tests were 2-sided. *P* values less than or equal to 0.05 were considered significant.

RESULTS

Trial profile. Of 1,052 patients screened, 622 were enrolled in the study (200 patients in France, 193 in Belgium, 129 in Switzerland, 65 in the US, and 35 in Austria) and randomly assigned to receive either CS (309 patients) or placebo (313 patients) (Figure 1). The cumulative time distribution of withdrawals was similar in the CS and placebo groups ($P = 0.4$ by log rank test), without significant differences in reasons for withdrawal. The duration of participation in the trial was similar in the CS group (mean ± SEM 608 ± 13 days, median 727 days) and the placebo group (mean ± SEM 620 ± 12 days, median 728 days; $P = 0.7$).

Patients in the 2 groups had similar demographic and baseline characteristics (Table 1). Compliance with the study treatment was good; for example, the percentages of patients who reported >90% drug intake at 24 months were 91% and 90% in the CS and placebo groups, respectively, with no significant difference between the 2 groups. The percentage of women who received hormone replacement therapy was similar in both groups at any time point (33% and 31% in the CS group and 39% and 35% in the placebo group at enrollment [$P = 0.3$] and 24 months [$P = 0.45$], respectively).

Radiographic measures. Figure 2 shows the average decrease in minimum JSW during 2 years of study. Because the distribution of minimum JSW values differed significantly from normality, comparisons for the main criteria were done using nonparametric tests and/or analyses of variance on the ranks of the values. The analysis of variance done on the ITT population showed both a significant effect of time ($P < 0.0001$ by Fisher's test) and a significant effect of the interaction

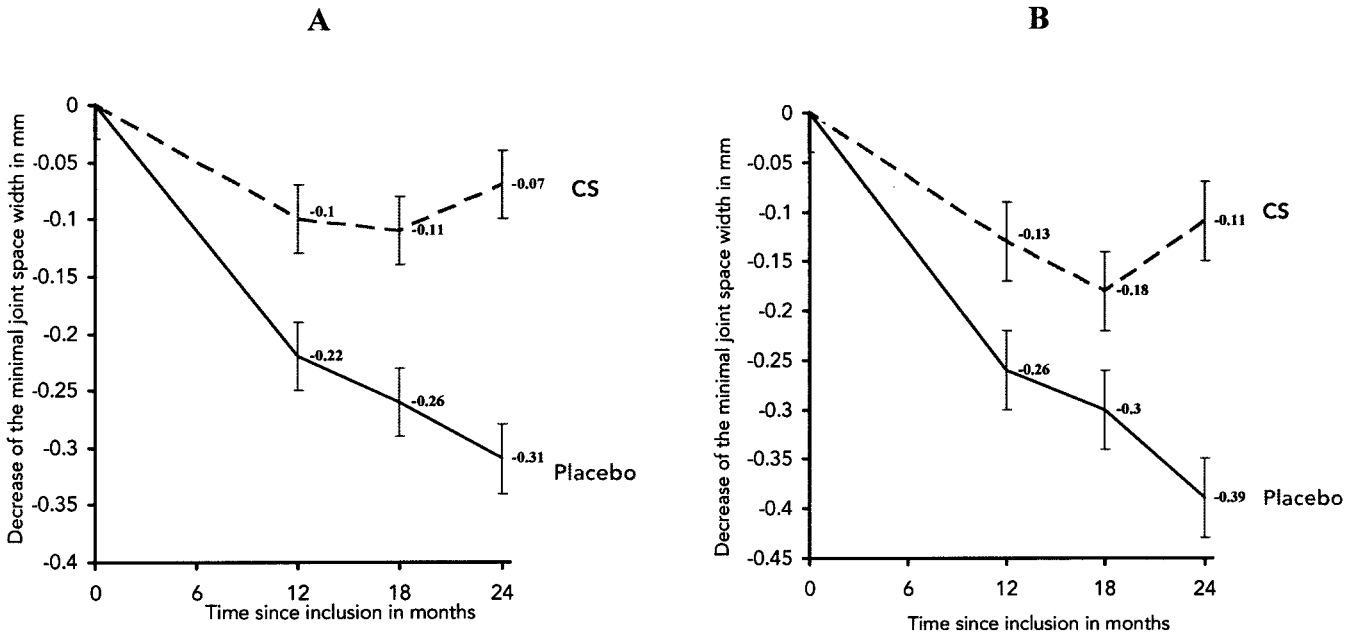

Figure 2. Change in minimum joint space width over time. **A,** Intent-to-treat analysis. **B,** Per-protocol analysis. Values are the mean ± SEM. CS = chondroitin sulfate.

between time and treatment effect ($P < 0.01$ by Fisher's test), which indicated that the effect of treatment significantly increased with time. The ITT analysis demonstrated a significant decrease in minimum JSW loss in the CS group (mean ± SEM −0.07 ± 0.03 mm) as compared with the placebo group (−0.31 ± 0.04 mm) between the time of study inclusion and month 24. The Hodges-Lehmann estimator of the median effect of treatment was 0.14 mm (95% CI 0.06–0.21 mm, $P < 0.0001$).

In the ITT analysis, the percentage of patients with radiographic progression (minimum JSW decrease of ≥0.25 mm) was significantly reduced in the CS group compared with the placebo group (28% versus 41%; $P < 0.0005$) (relative risk reduction 33% [95% CI 16–46%]). The number of patients needed to treat was 8 (95% CI 5–17). A similar statistically significant improvement with CS therapy was observed regardless of which threshold value between 0.05 mm and 0.7 mm was tested (Table 2).

Among initial patient characteristics, only the body mass index significantly interacted with treatment, with the effect of the treatment being more important in patients with a higher body mass index ($P = 0.03$).

At month 24, the percentage of patients with treatment failure according to the Group for the Respect of Ethics and Excellence in Science (GREES) criteria (19) was significantly lower in the CS group than in the placebo group (Table 3).

The per-protocol radiographic analysis confirmed a significant reduction in minimum JSW loss at 2 years in the CS group (mean ± SEM −0.11 ± 0.04 mm) as compared with the placebo group (−0.39 ± 0.04 mm). The Hodges-Lehmann estimator of the treatment effect was 0.20 mm (95% CI 0.11–0.30 mm, $P < 0.0001$). The percentage of patients with radiographic progression for the 0.25-mm threshold value was significantly reduced in the CS group compared with the placebo group (35% versus 48%; $P = 0.007$) (relative risk reduction 27% [95% CI 8–42%]). The number of patients needed to treat was 5 (95% CI 4–11). A similar statistically significant improvement with CS therapy was observed regardless of which threshold value between 0.05 mm and 0.7 mm was tested. At month 24, the percentage of patients who experienced treatment failure according to the GREES criteria was significantly lower in the CS group than in the placebo group, for minimum JSW decrease thresholds between 0.4 mm and 0.6 mm and an increase in the WOMAC pain score of 25%.

Symptoms. The ITT analysis (VAS and WOMAC subscale) demonstrated significantly faster improvement in pain in the target knee in the CS group

Table 2. Progressor analysis (JSW 0–0.7 mm), by ITT analysis*

JSW threshold	Day 1 to month 24		
	CS	Placebo	*P*
0.05 mm	139 (45)	180 (58)	0.002
0.10 mm	124 (40)	163 (52)	0.003
0.15 mm	114 (37)	151 (48)	0.004
0.20 mm	97 (30)	135 (43)	0.007
0.25 mm	85 (28)	128 (41)	0.0005
0.30 mm	78 (25)	125 (40)	<0.0001
0.35 mm	61 (20)	112 (36)	<0.0001
0.40 mm	53 (17)	104 (33)	<0.0001
0.45 mm	44 (14)	96 (31)	<0.0001
0.50 mm	41 (13)	81 (27)	<0.0001
0.55 mm	33 (11)	73 (23)	<0.0001
0.60 mm	31 (10)	72 (23)	<0.0001
0.65 mm	28 (9)	66 (21)	<0.0001
0.70 mm	26 (8)	57 (18)	0.0003

* Values are the number (%) of patients. JSW = joint space width; ITT = intent-to-treat; CS = chondroitin sulfate.

than in the placebo group ($P < 0.01$ for the interaction between time and treatment effect by analysis of variance on ranks) (Figure 3). Analysis at each period of the trial showed that for the decrease in pain scores (VAS), the differences between the 2 groups in favor of CS were significant between months 1 and 9.

The percentage of responder patients at 6 months, defined by a reduction in the pain score (VAS) of at least 40% or 60%, was significantly higher in the CS group than in the placebo group (53% versus 45% [$P = 0.04$] and 41% versus 32% [$P = 0.03$], respectively). The percentage of responder patients at 6 months, defined by a reduction in the pain score (VAS) of at least 40 mm or 60 mm, was significantly higher in the CS group than in the placebo group (28% versus 19% [$P = 0.01$] and 9% versus 4% [$P < 0.01$], respectively). The percentage of responder patients at 6 months, defined by a decrease in the WOMAC pain score of at least 40%, was significantly higher in the CS group than in the placebo group (41% versus 34% [$P = 0.05$]). The differences between groups in other symptom criteria (total WOMAC score, stiffness and physical function WOMAC subscale scores) did not reach statistical significance.

At 6 months, global efficacy (VAS) was better in the CS group than in the placebo group, as assessed by the patient (mean ± SEM 42.2 ± 1.8 mm, median 45, range 0–100 versus 36.6 ± 1.7 mm, median 32, range 0–100 [$P < 0.02$]) or the doctor (mean ± SEM 39.6 ± 1.6 mm, median 40, range 0–100 versus 34.8 ± 1.7 mm, median 29, range 0–100 [$P < 0.04$]).

The per-protocol analysis confirmed these results, with a significantly faster reduction in target knee pain in the CS group as compared with the placebo group. For the decrease in pain (VAS), the differences between the 2 groups in favor of CS were significant at month 6. The global efficacy (VAS) assessed by the patient at 6 months was better in the CS group as compared with the placebo group (mean ± SEM 46.1 ± 2.1 mm, median 50, range 0–100 versus 39.6 ± 2.2 mm, median 35, range 0–100 [$P = 0.03$]).

In the ITT analysis, cumulative consumption of acetaminophen during 2 years was limited, and no significant difference was shown between the CS group (mean ± SEM 165 ± 18 gm, median 32, range 0–1,903) and the placebo group (mean ± SEM 169 ± 17 gm, median 43, range 0–2,278 [$P = 0.5$ by nonparametric Wilcoxon's rank test). Consumption of NSAIDs was also limited: although not statistically significant, a trend toward a decrease in the cumulative consumption of NSAIDs after 2 years was observed in the CS group (mean ± SEM 189 ± 22 gm of ibuprofen equivalent, median 20, range 0–2,971) as compared with the placebo group (226 ± 24 gm of ibuprofen equivalent, median 31, range 0–2,251 [$P = 0.3$]). The per-protocol analyses confirmed these results.

Safety. Tolerability was assessed as very good or good by the majority of the patients in the CS and placebo groups (94% and 93% of subjects, respectively, at 24 months; $P = 0.6$). There were no significant differences between the CS and placebo groups in the frequency of adverse events during the clinical trial. Most of the adverse events were transient and mild. Gastrointestinal side effects were the most frequently reported (6% in the CS group and 5.9% in the placebo group). Adverse events were the cause of withdrawal in 16 patients (5%) in the CS group and 17 patients (5%)

Table 3. Treatment failure according to GREES criteria at month 24, by ITT analysis*

Threshold for decrease in JSW	Threshold increase in WOMAC pain score between day 1 and month 24					
	20%			25%		
	CS	Placebo	*P*	CS	Placebo	*P*
0.3 mm	127 (41.1)	160 (51.1)	0.01	119 (38.5)	157 (50.2)	0.004
0.4 mm	108 (35.0)	144 (46.50)	0.005	100 (32.4)	139 (44.4)	0.002
0.5 mm	98 (31.7)	131 (41.9)	0.009	89 (28.8)	125 (39.9)	0.004
0.6 mm	88 (28.5)	119 (38.0)	0.01	79 (25.6)	113 (36.1)	0.005

Values are the number (%) of patients. GREES = Group for the Respect of Ethics and Excellence in Science; ITT = intent-to-treat; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; JSW = joint space width; CS = chondroitin sulfate.

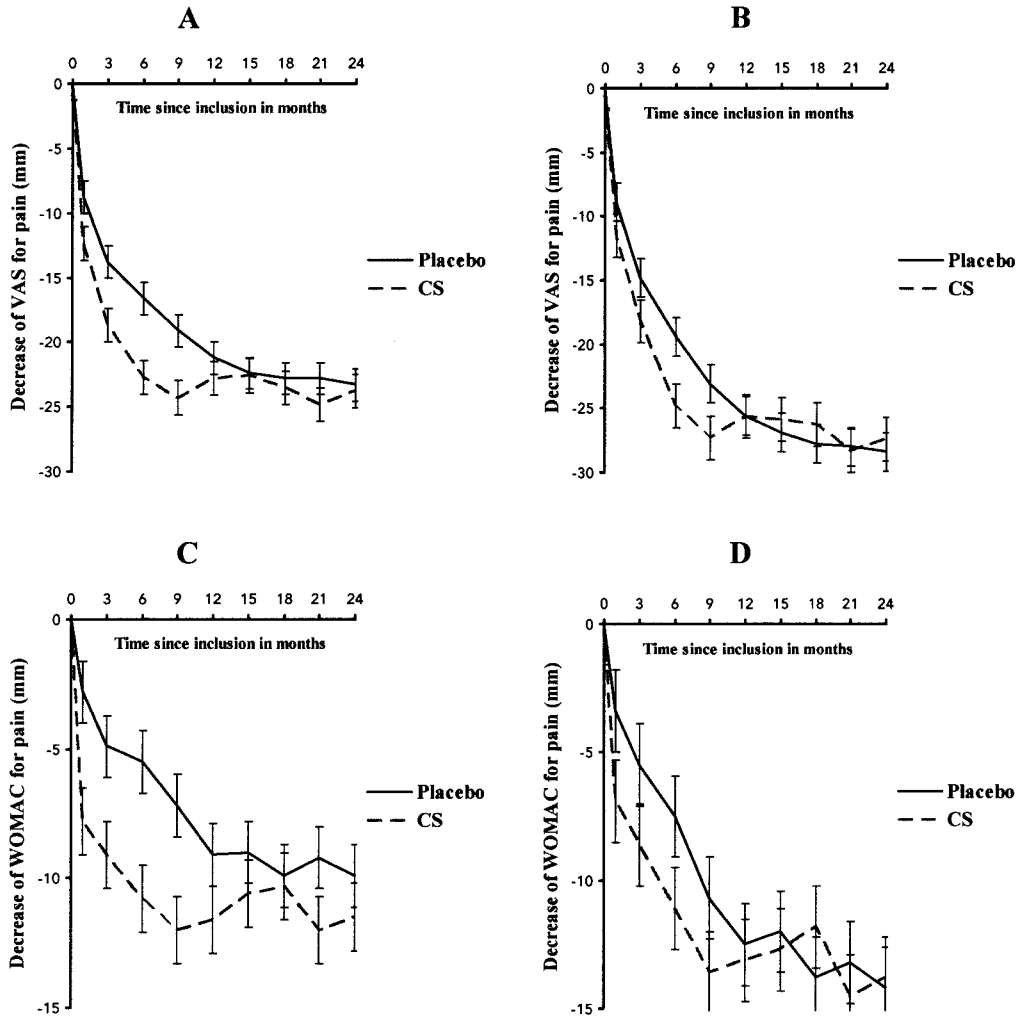

Figure 3. Change in pain over time. **A** and **B,** Pain as measured on a visual analog scale (VAS), by intent-to-treat (ITT) analysis (**A**) and per-protocol analysis (**B**). **C** and **D,** Pain as measured by the Western Ontario and McMaster Universities Osteoarthritis Index, by ITT analysis (**C**) and per-protocol analysis (**D**). Values are the mean ± SEM. CS = chondroitin sulfate.

in the placebo group (Figure 1). Routine laboratory tests did not show any significant abnormalities in the 2 groups.

DISCUSSION

We have demonstrated in the STOPP study that long-term administration of CS over 2 years can prevent joint structure degradation in patients with knee OA. The minimum JSW loss was significantly reduced in the CS group as compared with the placebo group. When individual joint space changes were analyzed, significantly fewer patients in the CS group had radiographic progression as compared with patients in the placebo group. CS also reduced pain as compared with placebo, confirming its symptom-modifying slow-acting effect for the treatment of OA.

The validity of the study is supported particularly by the consistent results of the ITT and per-protocol analyses, the relatively low dropout rate, the high quality of radiographic assessment, and the observed value for the average annual loss in minimum JSW in the placebo group, which is consistent with that observed in recent placebo-controlled studies (1,9–11).

Evaluation of a drug as a potential structure-modifying agent in OA requires an accurate and repro-

ducible measurement of JSW. In the present study, we used the Lyon schuss view. The main advantages of this technique include reproducible knee flexion, avoiding changes in patient positioning due to symptom modifications, good alignment of the medial tibial plateau with the x-ray beam, a reproducible image size of the knee, and better sensitivity to change (14,16,20). The good quality of radiographs obtained in the present study is shown by the intermargin distance of the medial tibial plateau of ≤1.3 mm at both baseline and the end point, which was obtained in 96% of patients.

Different validated methods were proposed for measuring minimum JSW, such as visual methods (using a caliper, ruler, or magnifying lens) and computed readings of digitized radiographs, which were suggested to decrease the number of observer-based errors (7,20–22). We used a validated method of digital image analysis to assess minimum JSW (16). Several long-term studies have shown that the rate of radiographic progression should be in the range of 0.1 mm/year (9–11,23). In the present study, the decrease in minimum JSW observed in the placebo group was in this range.

The protective effects of CS on minimum JSW loss observed in our study are consistent with the results of a recent study assessing the effect of 800 mg of CS (150 patients) or placebo (150 patients) administered for 2 years (11). Our study has important methodologic advantages over the latter trial, which included a significant proportion of patients with lateral tibiofemoral involvement or with a minimum JSW at inclusion of <1 mm; despite these limitations, this latter study showed a similar difference of 0.12 mm in minimum JSW loss between the CS and placebo groups (11).

In the present study, significantly faster improvement in pain was observed in the CS group as compared with the placebo group during the first 9 months. In contrast, no significant difference in pain between the 2 groups was observed during the second year. Several hypotheses may account for these variations. Only symptomatic patients were included, with a mean pain score (VAS) of 57 mm in both groups; thus, during the first 9 months of the study, the symptomatic effect of CS could be confirmed, as previously demonstrated in shorter (3–6 months) studies (24,25). A significant decrease in pain was also observed in the placebo group during the first year of the study, which may be partly attributable to the natural history of OA: at 12 months, the pain scores (VAS) in the CS and placebo groups were similar and low (mean ± SEM 31.5 ± 1.7 mm and 32.3 ± 1.6 mm, respectively). In these groups, in which a significant proportion of patients had absent or mild symptoms at 1 year, a further symptomatic effect of CS was unlikely to be observed. This symptomatic effect of CS, confirmed in our study, is in contrast with the results of a recent 24-week controlled study (the Glucosamine/Chondroitin Arthritis Intervention Trial [GAIT]) in which chondroitin sulfate and glucosamine HCl or their combination did not significantly reduce pain as compared with placebo in patients with knee OA (26). Several characteristics of the GAIT study may account for these discrepancies, including patient characteristics, study design, and outcome criteria (27).

Previous short-term studies have demonstrated that CS is fairly safe (24,25). No significant clinical or laboratory differences between the CS and placebo groups were observed in the present study.

Continuous therapy with CS at a dosage of 800 mg/day was used in the present study. Whether similar effects might be obtained with intermittent CS treatment, as suggested in a recent study (28), remains to be confirmed.

Whereas cartilage-unrelated effects might play a role in the relatively short delay in the action of CS on symptoms noted in short-term clinical trials, the long-term structural effects we demonstrated in this study might be attributable to the reported effects of CS on cartilage metabolism, including stimulation of anabolic activities and depression of catabolic activities (29–31).

Exogenous CS is absorbed as a high molecular mass polysaccharide together with derivatives resulting from a partial depolymerization and/or desulfation (32). After oral administration of CS, an increase in 4-sulfated disaccharide and the appearance of 6-sulfated disaccharide were observed in the plasma of healthy volunteers (32). Intestinal absorption in humans appears to be rapid, reaching a peak plasma level after 2–3 hours (13% as a high molecular weight product and 20% as a lower molecular weight component) (32).

The main limitation of this study is that we used a CS preparation that has been approved as a prescription drug; therefore, our results cannot be generalized to other chondroitin sulfate products (or compound mixtures) such as those available in some countries as dietary supplements.

A growing body of evidence suggests that the surrogate radiographic end point used in our study, i.e., reduced loss of minimum JSW, might be predictive of better OA outcomes, including the indication for joint surgery (33–35). Further studies with longer followup and different outcome criteria are warranted to assess whether the beneficial structural changes associated with

CS demonstrated in our study are predictive of improvement in the long-term clinical progression of OA.

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AUTHOR CONTRIBUTIONS

Dr. Kahan 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 design. Kahan, Uebelhart, De Vathaire, Reginster.
Acquisition of data. Kahan, Uebelhart, Reginster.
Analysis and interpretation of data. Kahan, Uebelhart, De Vathaire, Reginster.
Manuscript preparation. Kahan, Uebelhart, Delmas, Reginster.
Statistical analysis. De Vathaire.
Radiographic assessments. Delmas.

ROLE OF THE STUDY SPONSOR

IBSA and Genévrier Laboratories organized the data collection from each center and agreed to the study design defined by the principal investigator (AK), to the decision by the Scientific Committee (AK, DU, JYR) regarding selection of the center for radiographic measurements (PD), to the data analysis defined by the statistician (FdV) and the Scientific Committee (AK, DU, JYR), to the writing of the original manuscript by the principal investigator (AK) and of its final version approved by the Scientific Committee and the statistician (FdV), to submission of the manuscript for publication, and to the content of the submitted manuscript. Publication of this study was not contingent on the agreement of the study sponsor.

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