

Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo¹

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Summary

Objective: To investigate the efficacy and tolerability of a 3-month duration, twice a-year, intermittent treatment with oral chondroitin sulfate (CS) in knee osteoarthritis (OA) patients.

Design: A total of 120 patients with symptomatic knee OA were randomized into two groups receiving either 800 mg CS or placebo (PBO) per day for two periods of 3 months during 1 year. Primary efficacy outcome was Lequesne's algo-functional index (AFI); secondary outcome parameters included VAS, walking time, global judgment, and paracetamol consumption. Radiological progression was assessed by automatic measurement of medial femoro-tibial joint space width on weight-bearing X-rays of both knees. Clinical and biological tolerability was assessed.

Results: One hundred and ten of 120 patients were included in the ITT analysis. AFI decreased significantly by 36% in the CS group after 1 year as compared to 23% in the PBO group. Similar results were found for the secondary outcomes parameters. Radiological progression at month 12 showed significantly decreased joint space width in the PBO group with no change in the CS group. Tolerability was good with only minor adverse events identically observed in both groups.

Conclusion: This study provides evidences that oral CS decreased pain and improved knee function. The 3-month intermittent administration of 800 mg/day of oral CS twice a year does support the prolonged effect known with symptom-modifying agents for OA. The inhibitory effect of CS on the radiological progression of the medial femoro-tibial joint space narrowing could suggest further evidence of its structure-modifying properties in knee OA.

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Key words: Knee osteoarthritis, chondroitin sulfate, Lequesne's algo-functional index, joint space narrowing.

Introduction

Osteoarthritis (OA) is the most common form of arthritis in developed countries. The current treatment of OA is not aimed at cure but mainly at palliative management and includes physical, pharmacological and surgical

approaches. Most drug treatments have been developed to alleviate the symptoms of OA, mainly by reducing inflammatory processes and pain. There are two categories of symptomatic drugs for OA; the first are non-specific and rapidly acting such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) whereas the second are specific and slow acting with delayed onset of action (symptom-modifying agents). The rationale for using symptom-modifying drugs such as chondroitin sulfate (CS) as a treatment for OA disease was in part empirical based on the observation that CS decreased with aging and OA. Nevertheless, recent studies do support its administration such as the fact that the sulfation pattern of CS was found to be significantly altered in both OA cartilage, plasma and synovial fluid^{1,2}. Indeed it appears that exogenous chondroitin sulfate is absorbed as a high molecular mass polysaccharide together with CS derivatives originating from a partial depolymerization and/or desulfatation^{3–5}.

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Some studies regarding symptom-modifying agents were recently reviewed in two meta-analyses including both CS and glucosamine sulfate^{6,7}. Most clinical studies performed with CS were of short duration, generally 3–6 months^{8–11}. We previously reported a randomized, double-blind 1-year duration controlled pilot study that was performed on a small cohort of 42 patients¹². The patients were treated orally with 800 mg CS or with a placebo administered daily for 1 year. This limited study confirmed that CS was well-tolerated, significantly reduced pain and increased overall mobility capacity. In addition, in agreement with the American College of Rheumatology (ACR) recommendations^{13,14}, we also studied the potential structure-modifying effect of the drug¹². As with other symptom-modifying agents like glucosamine sulfate or hyaluronan, it is suggested that CS has a prolonged effect, which would justify an intermittent administration of the drug for the treatment of OA⁸. As a consequence, the authors set up a 1-year duration randomized, placebo-controlled study with two 3-month intermittent treatment periods with CS in patients with femoro-tibial OA. The primary aim of this study was to test the symptomatic efficacy of the drug, whereas the secondary aims were to assess both additional clinical parameters, radiological progression of knee OA using an automated measurement of the medial femoro-tibial joint space and measure some biochemical markers of bone and joint metabolism (this later part to be published in a separate article).

Methods

PATIENTS

A total of 120 patients of both gender, aged 40 and over and suffering from mono- or bi-lateral, clinically symptomatic idiopathic knee OA according to ACR criteria^{13,14} (patients suffering from knee pain and at least one of the three following criteria: age >40 years, stiffness <30 min, crepitus, as well as osteophytes) were enrolled between February 1996 and June 1998 in this multicenter study. Moreover only patients with a Kellgren and Lawrence radiological score of I–III with a minimum 25% remaining medial femoro-tibial joint space upon entry were selected. Incorporated patients were randomly allocated in equal numbers to one of the two treatment groups: chondroitin sulfate (CS) or placebo (PBO). All patients with other inflammatory joint diseases or systemic conditions affecting or involving the joints were excluded from the study. In addition, patients with the following conditions were also excluded from the study: primary or secondary neoplasias, bone metabolic diseases, and/or other metabolic or systemic diseases, patients undergoing various treatments such as intra-articular steroids, NSAIDs, symptom-modifying agents or bone-oriented therapies such as fluorides, bisphosphonates, calcitonin or patients under hormonal substitution taken within 3 months before the beginning of the study (wash-out period) were also excluded. The above treatments were also forbidden during the whole study duration.

All patients received complete information from the study physician before entering the trial and signed an informed consent sheet. The study protocol followed the rules of Good Clinical Practice and the Declaration of Helsinki and was reviewed and approved by multiple Independent Ethics Committees before the study began.

TREATMENT REGIMEN

The study design was double-blinded, placebo-controlled and all selected patients randomly allocated in one of two treatment groups. Patients in the CS group received Condrosulf[®] sachets (IBSA, Lugano, Switzerland) containing 800 mg of chondroitin 4&6 sulfate at a dose of 1 sachet/day taken every evening with a glass of water. Condrosulf[®] is a prescription drug containing highly purified chondroitin 4&6 sulfate of bovine origin in a concentration not inferior to 95%. Patients in the PBO group received placebo sachets containing 800 mg of vehicle administered on the same time schedule as for the CS group. Placebo and Condrosulf[®] sachets were packed in white anonymous sachets of identical appearance containing granules having the same aspect, odor and flavor.

The treatment was administered intermittently from entry to month 3 and between months 6 and 9. Patients of both groups received no treatment between months 3–6 and 9–12. Treatment compliance was established by asking the patients to return the remaining drugs supply. Each subject was free to take his own medication for co-existing diseases or conditions during the study with the exception of NSAIDs, symptom-modifying agents, steroids (oral or parenteral), bone-oriented therapies, (fluorides, bisphosphonates, calcitonin and hormonal substitution). Patients were free to take paracetamol (maximum 4 g/day) as rescue medication if needed, but they had to report the total amount of tablets taken in the daily diary. Study patients are required to stop the analgesic treatment (paracetamol) 24 h before every visit. The same physician evaluated each individual subject every 3 months throughout the study.

Treatments were assigned in blocks of six according to a computer generated randomization list. Investigators were provided with sealed envelopes, each marked with the corresponding patient number and containing the randomization code assigned to that patient. These envelopes were to be opened only in the event of an emergency.

OUTCOME MEASUREMENTS FOR EFFICACY

According to WHO/ILAR Guidelines for the evaluation of SYSADOA¹³, the following criteria were measured upon entry and during the study:

- The primary efficacy outcome criteria was the Lequesne's algofunctional index (AFI)¹⁵ at the end of the study. The AFI is a standardized and validated clinical instrument to evaluate pain and function in knee or hip OA patients. In patients with bilateral knee OA, the most symptomatic knee was selected as the study target knee.
- The secondary efficacy outcome criteria included the following additional clinical and radiological measurements.

The degree of spontaneous joint pain as assessed by the Huskisson's visual analogue scale (VAS) on a continuous scale of 0–100 mm¹⁶, the walking time evaluated as the minimum time in seconds necessary to perform a 20-m walk on a flat track course, the global judgment of efficacy as recorded by the patient and the physician on a semi-quantitative 4-point ordinal scale and the overall paracetamol consumption evaluating the number of tablets taken between two control visits.

Standard antero-posterior X-rays of the knees were performed in weight-bearing monopodal position upon entry and after 12 months of follow-up. Patients stood with

their knee fully extended and the film cassette was positioned as close as possible to the posterior surface of the joint. Patients were provided with hand support if required. The outline of the foot was drawn on a sheet of paper taped on the floor and the foot map was used to reposition the joint at the following examination. The X-ray film cassette was held in a vertical film holder with a film-to-focus distance of 110 cm. Radiographs of the knees were taken by the same trained observer at entry and at 12 months and used the reference atlas for the Kellgren and Lawrence qualitative score¹⁷. The medial femoro-tibial joint space width (JSW) was measured for both right and left knees by one observer blinded to the radiographic sequence with an image analysis computer (Mediscan®, Hologic, Inc.) according to a previously published method¹⁸. Briefly, the method includes a digitization of the X-ray and an automatic determination of a constant part of the medial femoro-tibial joint space. Within the demarcated area, the joint space contours are delineated by the operator. In this study, no target knee was defined at the beginning. The joint space surface area (JSSA), the mean joint space width (MeJSW) and the interbone distance at the narrowest point of the joint (minimum joint space width [MiJSW]) are automatically calculated. The reproducibility of the method has already been reported^{18–21}.

SAFETY AND TOLERABILITY OUTCOMES

Tolerability was assessed during overall study period at 3-month intervals by both patients and investigators using a 4-point verbal semi-quantitative judgment score. Any adverse event occurring during the treatment period was reported in the CRF. In addition, clinical laboratory evaluation was performed at the same times to assess the biological safety; these examinations included the determination of blood ESR, CRP, Hb, Ht, WBC, platelets and of the serum levels of bilirubin, urea and creatinine.

STATISTICAL METHODS AND DETERMINATION OF THE SAMPLE SIZE

The sample size population calculation was estimated according to previous clinical experience with oral CS treatment. Based on the hypothesis that the mean value of the Lequesne's index reduction after 1 year is by 40% for the Condrosulf® group and 20% for the Placebo group, considering a standard deviation of about 30% of the basal value for each group and performing the one way analysis of variance (in assuming $\alpha=0.05$, two-tailed, and $\beta=0.20$, that is a power of 80%), it would be necessary to analyze at least 80 patients (40 per group). Considering a drop out rate of about 30%, it would be necessary to enroll 120 patients (60 per group).

A descriptive statistical analysis including frequency of occurrence, mean±standard deviation (SD), minimum and maximum for all parameters was performed. The level of significance of the results was set at a P value=0.05. Age, weight and height were analyzed according to the Student t -test for unpaired data. Gender, concomitant or previous treatments, adverse events, concomitant treatments and dropouts were analyzed according to Yates corrected χ^2 for 2x2 tables.

The efficacy analysis was performed for the ITT population and the last observation carried forward (LOCF) method was used to replace missing values for the 26 drop out patients.

Pain levels and consumption of paracetamol were analyzed according to the Mann–Whitney U-test for non-parametric data.

Huskisson VAS, walking time, Lequesne's index and biological safety parameters were analyzed by ANOVA for repeated measures. For these variables, multiple comparisons were calculated according to Bonferroni's correction equation.

The knee radiological parameters have been analyzed by a standard Student's t -test and by ANOVA for repeated measures (the two knees of each subject were analyzed independently). Only the 'completers' with radiological data for one or two knees were included in this analysis. In addition, we used the analysis of the variation for each patient using the generalized estimating equations method (GEEM)^{22,23}. In the case of our radiological data, GEEM analysis allows to consider that the two knees of each patient are not independent, and no target knee has to be chosen. A total of 84 patients completed the 1-year study, but six of them did not perform X-rays at month 12 for personal reasons, therefore radiological evaluations were only available for 78 patients (39 in each treatment group).

Compliance analysis was performed with the non-parametric Mann–Whitney U-test. Judgment of efficacy and tolerability expressed by both physician and patient were analyzed according to the linear trend test. The statistical analysis of the results was carried out at the INSERM Unit 521 of the Gustave Roussy Institute, University of Paris XI, Villejuif, France.

Results

A total of 120 patients were randomized in the study. A total of 10 patients (six CS and four PBO) were lost to follow-up before month 3 (second control visit). Since they did not take any dose of treatment and did not report any data at the following control visit, they were consequently not included in the ITT analysis. Therefore, the 110 remaining patients (54 CS and 56 PBO) were included in the intent-to-treat statistical analysis (Fig. 1). A comparison of the baseline characteristics upon entry did not show any significant differences between both CS and PBO groups (Table I). A total of 26 patients (11 CS and 15 PBO) dropped out of the study between months 3 and 12 because of inefficacy, absence of compliance, increasing pain or various side effects. No statistically significant difference was shown between both groups. At the end of the study, at 12 months, the number of patients completing the study in the CS group was 43 and 41 in the PBO group.

PRIMARY EFFICACY OUTCOME CRITERIA

At entry, the mean score of the Lequesne's algorithm index (AFI), chosen as the primary outcome efficacy parameter, was not statistically different between both treatment groups: 9.0 ± 2.8 in the CS group vs 9.1 ± 3.2 in the PBO group. In the CS group, the AFI was decreased by 24, 25, 34 and 36%, at months 3, 6, 9 and 12, respectively. In the PBO group the mean AFI score showed less variations and was reduced by a total of 23% after 12 months (Table II). However, in both groups (CS and PBO), the mean decrease of AFI was statistically significant at each time point within each treatment group vs the mean basal value. An analysis of variance for repeated measures showed significant differences at month 9 and 12

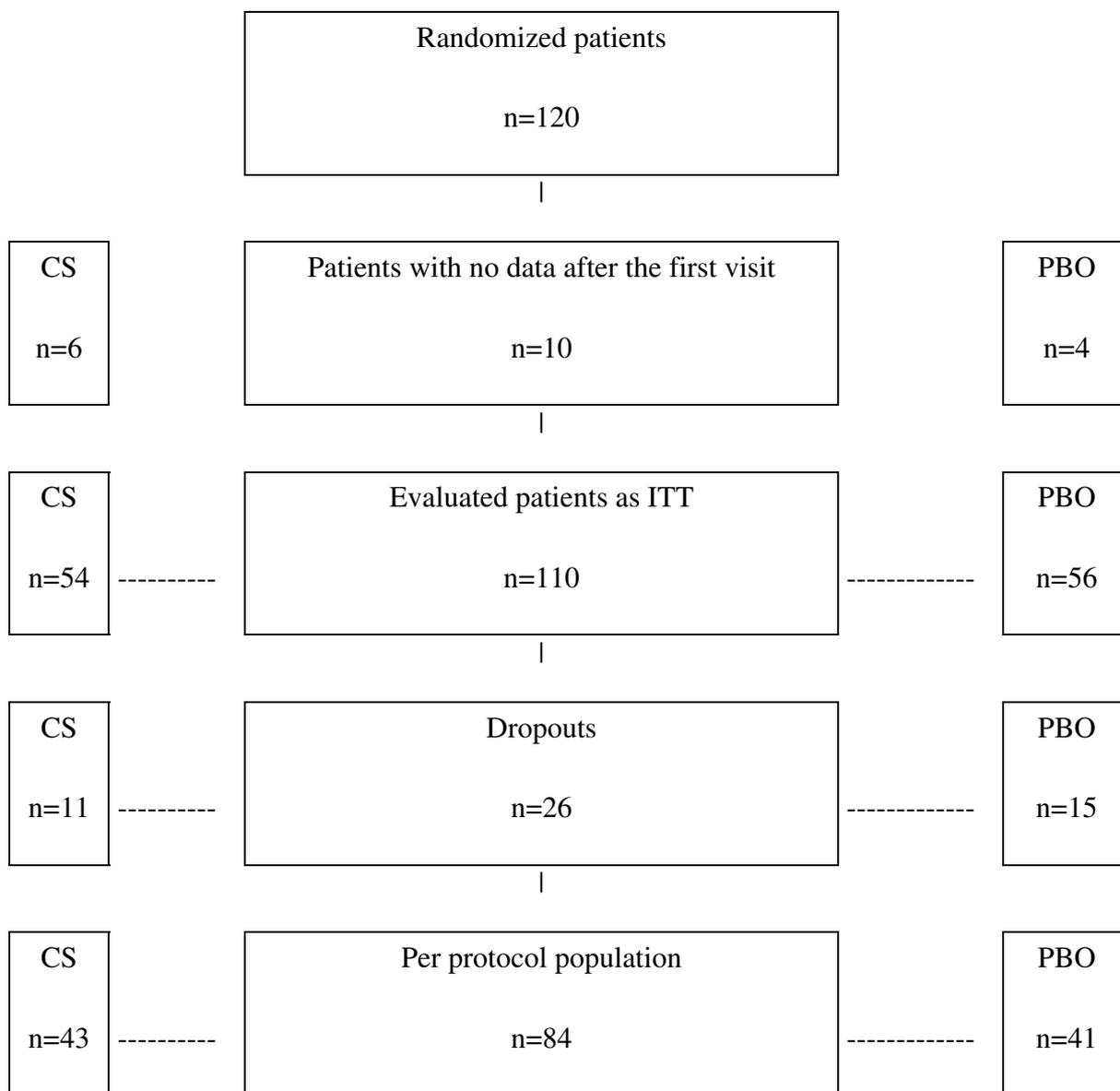


Fig. 1. Patient disposition and study course.

between the CS and the PBO groups, $P < 0.05$ and $P < 0.01$, respectively (Fig. 2).

SECONDARY EFFICACY OUTCOME CRITERIA

Regarding the second outcome efficacy parameters, at entry into the study, levels of spontaneous pain assessed by the Huskisson VAS were not significantly different: 58.8 ± 15.5 mm in the CS group vs. 61.1 ± 19 mm in the PBO group (Table II). The intensity of pain decreased respectively by 42% at month 9 and 12 in the CS group vs. 25% in the PBO group. Analysis of variance for multiple comparisons showed a significant difference between both treatment groups at month 9 and 12, $P < 0.05$.

The mean walking time showed no statistically significant difference between groups at baseline (24.5 ± 22.7 sec in the CS group vs. 22.8 ± 7.5 sec in the PBO group). A statistically significant reduction in the mean walking time

Table I
Characteristics of patients at entry (mean \pm SD)*

Group	CS (n=54)	PBO (n=56)	P (between groups)
Age (years)	63.2 \pm 9.1	63.7 \pm 8.1	NS
Gender (M/F)	11/43	10/46	NS
Weight (kg)	76.8 \pm 15.8	76.4 \pm 13.8	NS
K&L score (0/1/2/3/4)	(0/7/32/15/0)	(0/6/33/17/0)	NS
Huskisson VAS (mm)	58.8 \pm 15.5	61.1 \pm 19.0	NS
Lequesne's AFI	9.0 \pm 2.8	9.1 \pm 3.2	NS
Walking time (s)	24.5 \pm 22.7	22.8 \pm 7.5	NS
Symptom duration (months)	50.1	52.4	NS

* Abbreviations: CS=chondroitin sulfate; PBO=placebo; VAS=Huskisson visual analogue scale; AFI: Lequesne's algofunctional index; K&L=Kellgren & Lawrence.

Table II
Efficacy results (mean±SD): intention-to-treat analysis

Evaluation parameters	Control visits (month)	0	3	6	9	12
AFI						
CS (n=54)		9.0±2.8	6.8±3.6	6.7±3.5	6.0±3.8	5.8±3.6
PBO (n=56)		9.1±3.2	7.4±4.2	7.5±4.0	7.0±3.9	7.0±3.9
VAS (mm)						
CS (n=54)		58.8±15.5	42.9±23.2	40.5±23.9	34.0±26.4	34.3±27.4
PBO (n=56)		61.1±19.0	49.1±24.5	47.6±26.9	46.1±27.2	45.8±27.6
Walking time (s)						
CS (n=54)		24.5±22.7	21.4±9.0	21.5±9.4	20.9±8.0	20.1±6.8
PBO (n=56)		22.8±7.5	22.4±8.3	23.1±8.5	22.7±7.5	22.7±7.7

* P<0.05.

** P<0.01. ANOVA test between groups. CS=chondroitin sulfate; PBO=placebo; VAS=Huskisson visual analogue scale; AFI=Lequesne's algo-functional index.

Lequesne's Index (AFI) and VAS

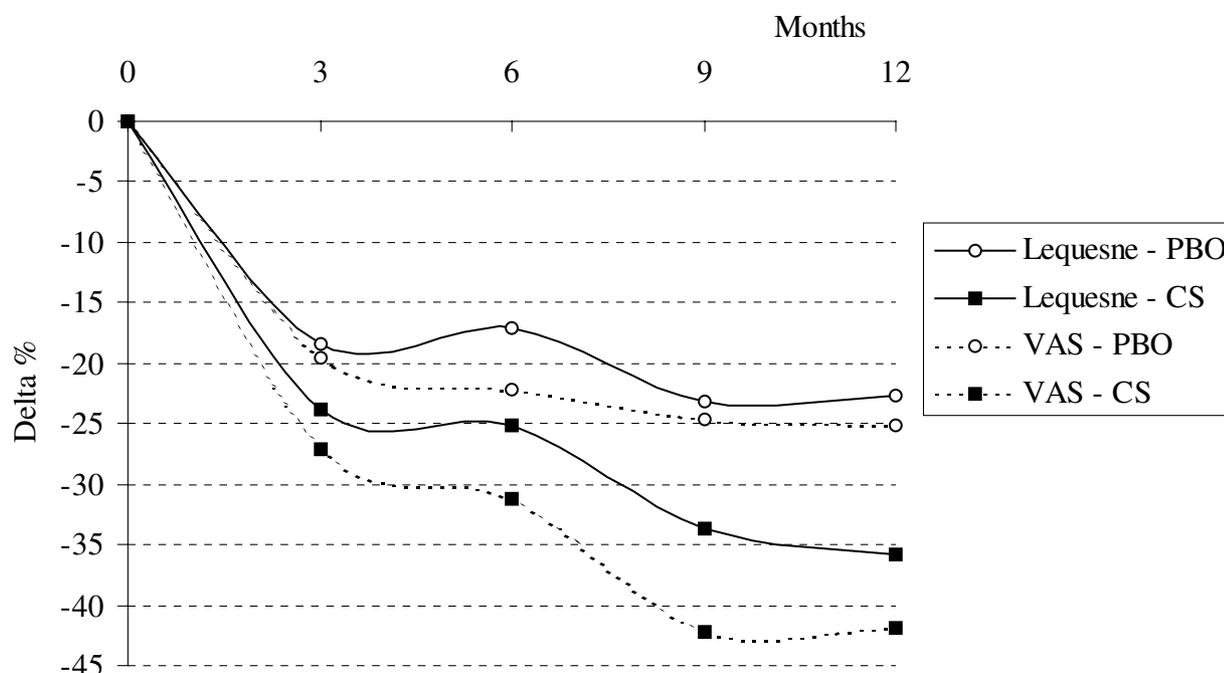


Fig. 2. Lequesne's algo-functional index (AFI) and Huskisson visual analogue score for pain (VAS) in delta %.

was observed in the CS group vs. the PBO group as of month 6 onwards ($p < 0.05$) and still improved with time until month 12 (Table II). The overall reduction in the CS group was 18% vs. 0.5% in the PBO group.

Both the physicians' and patients' overall efficacy assessment was very similar and significantly in favor of the CS group after respectively 6, 9 and 12 month observation periods ($p < 0.01$). At the end of the study by month 12, a total of 52% of the physicians' and patients' reported a global assessment of efficacy as "no effect" or "fair" in the PBO group vs. 11% in the CS group. In sharp contrast, the physicians' and patients' overall efficacy evaluation was reported as "good" and "very good" in 89% of the CS

patients as compared to 13% "very good" results and 36% reported "good" results in the PBO group.

During the first month of treatment, the mean consumption of paracetamol tablets was equivalent in the two groups (21.6±26.7 in the CS group vs. 22.0±24.2 in the PBO group). In the following periods, between months 1–3, 3–6, 6–9 and 9–12, the mean paracetamol consumption was always significantly greater in the PBO group ($P < 0.05$) as compared with the CS group (25.8±37.0 in the CS group vs 55.5±68.1 in the PBO group at month 12).

The investigational drugs returned at each control visit, were considered to reflect the compliance with the treatment. No significant difference in the compliance with the

Table IIIA
Evolution of the medial femoro-tibial joint space narrowing: left+right knees pooled (mean±SD)

Months	CS (n=77)*	P (t-test) (within group)	PBO (n=76)*	P (t-test) (within group)	P (ANOVA) (between groups)
Joint space surface area (JSSA) (mm ²)					
0	68.0±27.2		63.3±24.4		At baseline: NS
12	67.8±26.9	NS	58.7±20.9	P<0.01	Evolution: NS
Minimum joint space width (MiJSW) (mm)					
0	3.65±1.46		3.54±1.39		At baseline: NS
12	3.61±1.51	NS	3.23±1.27	P<0.01	Evolution: P<0.05
Mean joint space width (MeJSW) (mm)					
0	4.20±1.51		4.03±1.47		At baseline: NS
12	4.20±1.58	NS	3.74±1.28	P<0.01	Evolution: P<0.05

*Only the X-ray of one knee was available for one patient belonging to CS group and for two patients belonging to PBO group.

Table IIIB
Mean and 95% CI change in joint space narrowing

	CS (n=77)	PBO (n=76)	Difference (95% CI)	P (t-test)
JSSA (mm ²)	-0.19 (-3.56 to 3.17)	-4.55 (-8.61 to -0.49)	4.36 (-0.19 to 8.91)	0.060
MiJSW (mm)	-0.04 (-0.23 to 0.14)	-0.32 (-0.57 to -0.07)	0.27 (0.004 to 0.55)	0.047
MeJSW (mm)	-0.006 (-0.20 to 0.18)	-0.29 (-0.53 to -0.04)	0.28 (0.01 to 0.55)	0.039

treatment was observed between groups (mean returned tablets±SD at control visit month 3: CS group: 4.4±6.4; PBO group 4.3±7.7 corresponding to about 93% compliance for both groups; at control visit month 9: CS group: 2.1±3.6; PBO group 2.0±4.5 corresponding to about 98% compliance for both groups).

Upon entry, the Kellgren and Lawrence (KL) radiological qualitative score was not significantly different between both CS (mean±SD: 2.28±1.09) and the PBO (mean±SD: 2.36±1.09) groups (Table I). At the end of the study period, the mean KL score was unchanged (2.29±1.02 in the CS group vs 2.45±1.06 in the PBO group). A quantitative radiological evaluation was also performed on the knee X-rays using two successive statistical methodologies. At first, both right and left knees were analyzed separately and following variables measured: the joint space surface area (JSSA), mean joint space width (MeJSW) and minimum joint space width (MiJSW). Upon entry, these variables were not significantly different between the CS and PBO groups. At the end of the study, all three variables were significantly decreased in the PBO group (P<0.01), whereas no significant changes could be observed in the CS group (Table IIIA). Table IIIB shows the results expressed as mean and difference 95% CI change in JSW in the different groups, with P values based on t-test analysis. The generalized estimating equation method (GEEM), which is an extension of the generalized linear models, was used as an additional tool to analyze the data. Indeed, GEEM allows us to treat each patient's data without having to pre-select a target knee. This analysis showed that, as compared to placebo, CS treatment had a significant role upon the variation of JSSA (0.065±0.031; P=0.03) and MeJSW (0.031±0.017; P=0.03), but not for MiJSW (0.028±0.020; P=0.1).

SAFETY/TOLERABILITY EVALUATION

Only minor adverse events (AEs) occurred during this 1-year study. Those possibly related to the treatment were gastrointestinal (epigastralgia, pyrosis and nausea) and occurred in both CS and PBO groups with a frequency of four and six events respectively. Two dropouts (1 CS, 1 PBO) occurred during the study due to epigastralgia, while one patient of the CS group stopped the treatment after 9 months because of vertigo.

Clinical laboratory evaluations did detect some minor changes in the serum levels of bilirubin by month 9 and serum urea levels at months 9 and 12 in the PBO group. No modifications were observed in any other clinical chemistry or hematological variables except for an isolated ESR increase in the PBO group by month 12.

The global assessment of tolerability expressed by both the patients and the physicians was very similar and no difference was observed between the two groups except for a significantly better tolerability score for the CS group after 1 month of treatment.

Discussion

This original study presents the results of a 1-year clinical trial conducted in knee OA patients receiving oral CS given on a 3-monthly intermittent basis, twice yearly. Based upon the present results, the following comments can be addressed.

At first, this study, specifically powered to assess the clinical effects of CS on pain and function as a primary efficacy outcome, is a confirmation of previous results obtained with oral CS used for the treatment of human

OA^{8-12,24}. Both AFI, VAS, walking time and analgesic consumption support the fact that CS is a symptom-modifying agent, which acts with a delayed onset of action and does improve both the painful symptoms and the function of knee OA patients^{13,25,26}.

In addition, this trial confirmed that CS administered orally at a dose of 800 mg/day on an intermittent basis for three months twice a year does have a prolonged effect. This specific effect is a characteristic of the symptom-modifying agents as well as their delayed onset of activity^{25,27}. These characteristics have already been well documented and confirmed in previous studies using oral CS, but administered on a regular daily basis for periods extending from 3 up to 12 months^{8,24}. The prolonged therapeutic effect observed in this intermittent study is a novel element regarding the mode of action of oral CS. A potential limiting factor of the study could be that the comparison was performed between both CS and PBO groups, but did not include a third group of OA patients receiving a continuous 1-year daily CS treatment.

The third important finding deals with the potential structure-modifying properties of the compound²⁶. This effect was previously suggested in one animal study²⁸ and two clinical studies including patients with knee OA¹² and finger OA^{29,30}. In the knee OA trial¹² we found that treatment with CS was also associated, in a group of patients, with an absence of change of the medial femoro-tibial joint space width whereas joint space narrowing did occur in the placebo-treated patients. The femoro-tibial joint space measurements obtained in this study suggest that CS treatment might influence the structural progression of knee OA over 1 year. In addition, GEEM analysis was a further confirmation of a significant reduction of the femoro-tibial joint space narrowing due to CS treatment in two out of three measured radiographic variables. It must be stated that minimum JSW represents the most sensitive measurement of joint space narrowing, but this is only true in the case of postero-anterior X-rays of the knee joint where the tibial plate is horizontal. In our study, the horizontal positioning of the tibial plate was not checked, but it was certainly not optimal as the performed X-rays were antero-posterior. Even if the X-ray procedure would now be using postero-anterior projection of the knee joint, this clinical trial nevertheless represents a further validation for the non-invasive measurement of joint space narrowing using standardized x-rays and digitized automatic radiographic computerized equipment^{18,20}. As recently shown with glucosamine sulfate, some symptom-modifying agents do have interesting chondroprotective properties, which can be assessed non-invasively by quantitative radiography³¹⁻³³.

A controversial issue with oral CS treatment is often the actual oral absorption of the drug. In a recent study⁵, CS (Condrosulf[®]) was orally administered to 20 healthy human volunteers, and CS derivatives were extracted and purified from plasma over 48 h. After oral administration of Condrosulf[®], CS plasma levels increased by more than 200%. Absorption of exogenous CS was also proved by the actual changes in the composition of CS derived disaccharides in plasma after drug administration as compared to baseline.

Importantly, the excellent clinical and biological profile of tolerance of the drug observed in our study did also confirm the good safety profile of oral chondroitin sulfate^{6-10,12,34,35}. This tolerability profile might be decreased by the intake of CS sold as a nutraceutical as recently reported by Danao-Camara³⁶. As a consequence,

these authors insisted on the necessity of an optimal source and a high quality of CS needed for human use. This particular safety trend does also strongly support the conduct of future larger and longer chondroprotection trials³⁷.

Conclusion

This study supports the evidence that oral CS of bovine origin and high pharmaceutical quality (Condrosulf[®]) is a well-tolerated drug, which is effective in reducing pain and improving function in patients suffering from symptomatic knee OA. The intermittent treatment schedule of 800 mg/day for 3 months, twice a year could certainly be recommended for patients presenting with low and/or medium grade knee OA based upon our clinical results and the observed prolonged therapeutic effect of the drug. In addition, our results on those OA patients who completed the trial might support the hypothesis of earlier studies and present additional arguments for CS also to be considered as a structure-modifying drug for OA. Regarding this particular issue, results of longer duration and larger trials should ultimately provide the clues regarding the effectiveness of CS as a structure-modifying drug for the treatment of knee OA.

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