Osteoarthritis and Cartilage (1998) **6**, (Supplement A), 25–30

1063–4584/97/030025 + 06 $12.00/0

OSTEOARTHRITIS and CARTILAGE

Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3×400 mg/day vs placebo

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Summary

This multicenter randomized, double-blind, controlled study was performed to compare the efficacy and tolerability of chondroitin sulfate (CS, Condrosulf®, IBSA, Lugano, CH) 1200 mg/day oral gel vs CS 3×400 mg/day capsules vs placebo, in patients with mono or bilateral knee osteoarthritis (Kellgren and Lawrence radiographic score grade I to III). A total of 127 patients, 40 of whom were treated with CS 1200 mg/day, 43 with CS 3×400 mg/day and 44 with placebo, were included in the statistical analysis of this 3-month treatment study. In the CS groups, Lequesne's Index and spontaneous joint pain (VAS) showed a significant reduction of clinical symptoms ($P < 0.01$ for both parameters), while only a slight reduction was observed in the placebo group (P = ns for Lequesne's Index and $P < 0.05$ for VAS).

The physician's and patient's overall efficacy assessments were significantly in favour of the CS groups ($P < 0.01$). The treatment carried out with the three formulations was very well tolerated.

In conclusion, these results indicate that CS favours the improvement of the subjective symptoms, improving the joint mobility. An additional consideration is that the efficacy of 1200 mg CS as a single daily dose does not differ from that of 3×400 mg daily doses of CS for all the clinical parameters taken into consideration.

Key words: Chondroitin sulfate, Knee osteoarthritis, Lequesne's Index.

Motive of the study

Chondroitin sulfate (Condrosulf®, IBSA, Lugano, Switzerland) administered at a dosage of 1200 mg divided into three doses per day has now become a part of the therapeutic armoury of the French rheumatologist. If the quantity of active-drug could be absorbed following administration of a single daily dose, this would enhance the patient's compliance.

Aim of the study

The aim of this trial was to assess the efficacy and tolerability of a new presentation of chondroitin sulfate CS 4&6, in sachets of oral gel at 1200 mg (CS 1200) as a single daily dose, vs three daily doses of chondroitin sulfate CS 4&6 in capsules of 400 mg (CS 3×400) and vs a placebo (PBO).

Supplement sponsored by IBSA (Switzerland)/Laboratoires GENEVRIER (France).

Methods

This was a 3-month phase III, randomized, double-blind, double-dummy, in parallel groups clinical trial. The sample size was estimated to be 40 patients/group (CS 1200 group, CS 3×400 group and placebo group).

PATIENTS

Outpatients of either sex, aged > 45 years, with femoral-tibial knee osteoarthritis, internal or external (according to Altman criteria, ACR), unilateral or bilateral, of stages I to III, which implies conservation of an articular joint space, and requiring the stable daily administration of one of the authorized NSAIDs for at least 1 month before the trial, were eligible for the trial.

Patients with peptic gastroduodenal ulcers, renal dysfunction, or severe organic diseases as well as pregnant and lactating women were excluded from the study.

Medications for co-existing diseases or conditions could be administered during the study with the exception of SYSADOA, steroids (oral or parenteral), bone-oriented therapies (fluoride, biphosphonates, calcitonin, hormonal substitution).

All patients gave their written informed consent to participate in the study, which was carried out in accordance with the Helsinki Declaration and its subsequent amendments.

TEST DRUGS, DOSAGE AND ADMINISTRATION

To preserve the double blind condition of the study, chondroitin sulfate CS 4&6 oral gel at 1200 mg (CS 1200) and placebo oral gel were available in sachets of identical appearance, as well as chondroitin sulfate CS 4&6 capsules of 400 mg (CS 3×400) and placebo capsules.

During the 3 months of the study, patients assigned to the CS 1200 group took one sachet of oral gel CS at 1200 mg and one placebo capsule in the morning, then one placebo capsule at noon and one placebo in the evening.

Patients assigned to the CS 3×400 group took one sachet of placebo oral gel and one capsule of 400 mg CS in the morning, one capsule of 400 mg CS at noon and one capsule of 400 mg CS in the evening.

Patients assigned to the placebo group took one sachet of placebo oral gel and one placebo capsule in the morning, one placebo capsule at noon and one placebo capsule in the evening.

During the 3-month study, patients were allowed to take authorized NSAIDs if necessary and the daily consumption was recorded. The NSAIDs consumption was arbitrarily calculated as Diclofenac equivalent, considering that 150 mg of Diclofenac was equivalent to 900 mg of Alminoprofen, 400 mg of Etodolac, 300 mg of Flurbiprofen, 2400 mg of Ibuprofen, 100 mg of Indometacin, 300 mg of Ketoprofen, 1000 mg of Naproxen, 20 mg of Piroxicam, 1100 mg of Sodium Naproxen and 20 mg of Tenoxicam.

Visit schedule and assessments

The duration of the treatment foreseen by the protocol was 3 months (91 days) during which four clinical visits were fixed, at day 0 (D0, inclusion), D14, D42 and D91. The efficacy evaluation criteria were:

- Principal criterion:
  - algo-functional Lequesne's Index
- Secondary criteria:
  - spontaneous pain on a visual analog scale (VAS) of 100 mm
  - consumption of authorized NSAIDs during the treatment, calculated as Diclofenac equivalent (see 'Test drugs, dosage and administration')
  - overall judgement of both physician and patient.

STATISTICAL ANALYSIS

1. Comparison between groups:
   Comparison between the included groups was verified in using the Kruskall–Wallis nonparametric test, for the comparison of three groups regarding quantitative variables and the chi-square test of heterogeneity for qualitative variables.
2. Efficacy and tolerance criteria:
   The investigation of efficacy and tolerance was carried on all of the included patients (intention-to-treat analysis), in taking into account the last known value. The following two comparisons had been made:

- Chondrosulf 1200 mg/day versus placebo
- Chondrosulf 3×400 mg/day versus placebo

A comparison of the evolution of the Lequesne's Index, of the visual analog scale and of the consumption of NSAIDs between day 0 and day 91, or between day 0 and the last known value, was

Table I
Patient's characteristics

	CS 1200 Chondroitin sulfate oral gel 1200 mg/day	CS 3×400 Chondroitin sulfate capsules 3×400 mg/day	PBO Placebo	*P* value
No. of patients at entry	40	43	44	
Men/women	16/26	8/34	7/37	0.09
Age (mean ± S.D.)	63 ± 11	63 ± 9	64 ± 8	0.7
Weight (mean ± S.D.)	76 ± 14	72 ± 13	78 ± 16	0.9

Table II
Clinical status of the knee osteoarthritis in 127 patients at inclusion

Evaluation parameters	CS 1200 ($n=40$)	CS 3×400 ($n=43$)	Placebo ($n=44$)	P value
Lequesne				
Mean values (S.D.)	11 (3)	10 (3)	10 (3)	0.7
Median values (min–max)	11(4.5–18.5)	10 (5–16)	10 (5–18)	
VAS (mm)				
Mean values (S.D.)	58 (13)	54 (12)	56 (13)	0.7
Median values (min–max)	61 (30–80)	55 (30–80)	56 (30–80)	
right	13	14	16	
left	9	13	10	0.9
bilateral	18	16	18	
Symptomatic since (years)				
Mean values (S.D.)				
right	6 (5)	4 (4)	6 (5)	0.3
left	5 (5)	5 (4)	6 (5)	0.7
Median values (min–max)				
right	4 (0.7–25)	3 (1–15)	5 (1–20)	
left	3 (0.7–25)	5 (1–15)	4 (1–20)	

carried out with a nonparametric test according to the progressive response of each patient.

A comparison of the evolution of the tolerance score between day 0 and day 91, or between day 0 and the last known value, was carried out with the Mantel–Haenzsel chi-square test on the score value at day 0.

The evolution during the period of these judgement criteria was compared by the analyses of variance for repeated measurements on the rank variables. In addition, inside each of the three test groups, the statistical significance of the evolution during the period of the judgement criteria was tested by means of Wilcoxon's test for paired comparisons.

Results

A total of 127 patients, 40 of whom were treated with CS 1200, 43 with CS 3×400 and 44 with placebo, were included in this study (Table I). At baseline, the three groups were well balanced for sex, age, weight and height.

The clinical status of the knee osteoarthritis was comparable between the three groups of treatment (Table II).

LEQUESNE'S INDEX

The score for Lequesne's Index decreased in the three groups from D0 to D91 (Table III). The reduction of the index was constant in the two CS groups between D0 and D91, about 40–45% of its initial value, whereas in the PBO group it was approximately 10% of its initial value (Fig. 1).

Statistically, at D91 this reduction was significantly greater in the two CS groups than in the PBO group ($P < 0.0001$), it was already significant at D14 in the CS 1200 group ($P < 0.05$) and it became significant at D42 in the CS 3×400 group ($P < 0.001$). There was no significant difference between both CS groups for this criterion.

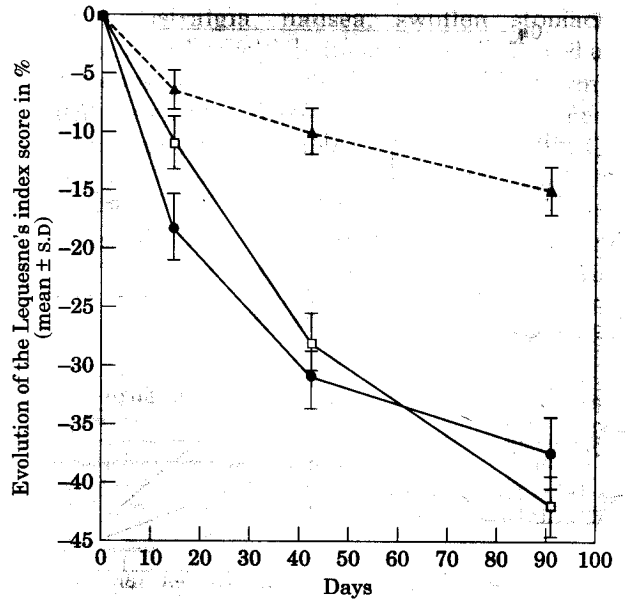

FIG. 1. Evolution of the Lequesne's Index score in % (mean ± S.D.). –●– = CS 1200; –□– = CS 3×400; --▲-- = PBO.

Table III
Scores registered for the parameter 'algo-functional Lequesne's Index' at D0, D14, D42 and D91 in the different treatment groups

Algo-functional Lequesne's Index		CS 1200 ($n=40$)	CS 3×400 ($n=43$)	Placebo ($n=44$)	P value (Wilcoxon-test)
D0	mean values (S.D.)	11 (3)	10 (3)	10 (3)	0.5
	median values (min–max)	11 (4.5–18.5)	10 (5–16)	10 (5–18)	
D14	mean values (S.D.)	9 (3)	9 (3)	10 (3)	0.4
	median values (min–max)	9 (1–14)	9 (5–16)	10 (2.5–17)	
D42	mean values (S.D.)	7 (3)	7 (2)	9 (3)	0.0005
	median values (min–max)	7 (0.5–14)	7 (2–13)	9 (2.5–18)	
D91	mean values (S.D.)	6 (3)	6 (3)	9 (4)	0.0001
	median values (min–max)	6 (1–12)	6 (1–13)	9 (2.5–19)	

Table IV
VAS scores at D0, D14, D42 and D91 in the three treatment groups

VAS of the pain (mm)		CS 1200 ($n=40$)	CS 3×400 ($n=43$)	Placebo ($n=44$)	P value (Wilcoxon-test)
D0	mean values (S.D.)	58 (13)	54 (12)	56 (13)	0.4
	median values (min–max)	61 (30–80)	55 (30–80)	56 (30–80)	
D14	mean values (S.D.)	44 (19)	47 (16)	52 (16)	0.1
	median values (min–max)	45 (5–76)	49 (6–90)	50 (20–83)	
D42	mean values (S.D.)	35 (17)	37 (18)	50 (18)	0.0009
	median values (min–max)	37 (5–78)	41 (1–76)	50 (2–87)	
D91	mean values (S.D.)	29 (16)	28 (19)	45 (19)	0.0001
	median values (min–max)	26 (5–60)	26 (0–70)	48 (0–80)	

VISUAL ANALOG SCALE (VAS)

Table IV shows the levels of pain as measured by the visual analog scale (VAS) in the three groups during the four visits. The decrease in VAS was constant between D0 and D91 in the two groups treated with CS, whereas it was limited to the first 14 days for the subjects treated with PBO (Fig. 2); measured in millimetres, the average reduction of

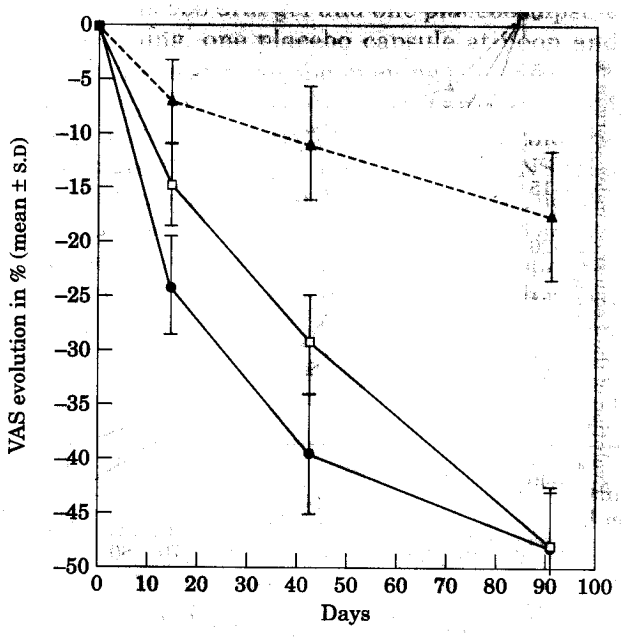

FIG. 2. VAS evolution in % (mean ± S.D.).–●– = CS 1200; –□– = CS 3×400; --▲-- = PBO.

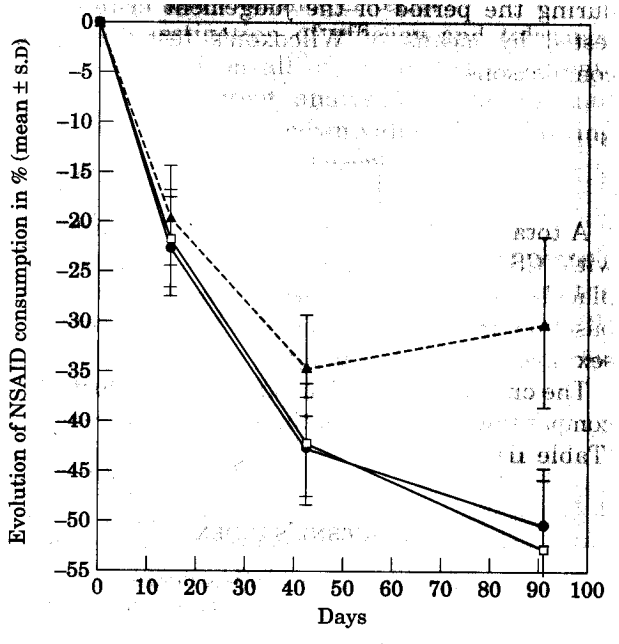

FIG. 3. Evolution of NSAID consumption in % (mean ± S.D.). –●– = CS 1200; –□– = CS 3×400; --▲-- = PBO.

Table V
Efficacy judgements expressed as a percentage by the physicians and patients

	Physicians				Patients			
	D42		D91		D42		D91	
	Poor–fair	Good–very good	Poor–fair	Good–very good	Poor–fair	Good–very good	Poor–fair	Good–very good
CS 1200 ($n=40$)	32	68	31	69	32	68	29	71
CS 3×400 ($n=43$)	40	60	29	71	33	67	34	66
PBO ($n=44$)	64	36	66	34	62	38	66	34

the VAS was almost the same for the two CS groups (29 and 26 mm respectively), and it was a little more rapid in the CS 1200 group, whereas average reduction of VAS in the PBO group was only 10 mm.

Statistically, at D91, this drop was significantly greater than in the PBO group (group CS 1200 $P < 0.0001$, group CS 3×400, $P < 0.0005$). Significance was reached for the CS 1200 as from D14 ($P < 0.01$) and from D42 for the CS 3×400 group ($P < 0.005$).

DAILY CONSUMPTION OF AUTHORIZED NSAID

The reduction in consumption of authorized NSAIDs was anevaluation parameter of the treatment's efficacy. Measured in diclofenac equivalent, the reduction of the average daily consumption between D0 and D91 was 58 mg in the group treated with CS 1200, 56 mg in the group treated with CS 3×400, and 34 mg in the group administered PBO. All of these reductions are significant.

The statistical comparison between groups shows that the reduction of the daily consumption of authorized NSAIDs was greater in the subjects treated with CS 1200 and CS 3×400 than in the subjects who received PBO (CS 1200 vs PBO: $P < 0.06$, CS 3×400 vs PBO: $P < 0.08$).

There was no significant difference in consumption of NSAIDs between the two CS groups at any of the times D14, D42 and D91.

Figure 3 represents the percentage evolution of NSAID consumption.

OVERALL JUDGEMENT OF THE TREATMENT EFFICACY

The efficacy of the treatment has been judged by the physician and the patient on a four point verbal scale: none, mediocre, good and very good.

Concordance of judgements between physicians and patients was very good; their judgement is described in Table V.

There is a significant difference between chondroitin sulfate treatments (CS 1200 and CS 3×400) and the placebo: at D42 $P < 0.05$, and at D91 $P < 0.01$.

On the other hand, there is no difference in efficacy between the treatments CS 1200 and CS 3×400, either at D42 or at D91.

OVERALL JUDGEMENT OF TREATMENT TOLERABILITY

Tolerability to the three treatments, judged by both the physician and the patient, was very good.

ADVERSE DRUG EVENTS (ADES)

The occurrence of adverse drug events (ADEs) was reported in 28 cases (Table VI). Undesirable effects were, above all, digestive troubles: 21 cases, 10 of which belonging to the placebo group reported gastralgia, nausea, swollen stomach, vomiting, diarrhea which, in most cases, cleared up spontaneously or were resolved by classic symptomatic treatment. They have led to treatment suspension in six cases (one in CS 1200, two in CS 3×400, three in PBO). A few cutaneous manifestations, four in total of pruritus or prurigi- nous eruption, were responsible in two cases of drop-out. Other ADEs, such as edema of the ankle,

Table VI
Adverse drug events that occurred during the trial period

Type of ADE	CS 1200 ($n=40$)	CS 3×400 ($n=43$)	Placebo ($n=44$)
Digestive	4	7	10
Cutaneous	1	1	2
Edema of the ankle	0	1	0
Falling hair	1	0	0
Extrasystoles	0	1	0
Total	6	10	12

extra systoles and falling hair were reported by three patients.

Discussion

The results derived from several previous clinical trials, which evidenced the retarded [1–3] and lasting [4–6] action of the effects of chondroitin sulfate 4&6 beyond the study end strongly suggested that taking the drug in a single daily dose of 1200 mg would have similar efficacy to that of three doses of 400 mg. This assumption was confirmed by the trial. The good tolerability of CS oral gel has also been tested: adverse drug events were reported only in 28 cases. The number of ADEs was lower in the CS 1200 group (6 cases) than in the CS 3×400 group (10 cases) and in the PBO group (12 cases); most of ADEs seemed to be related to the associated treatment with NSAIDs, often responsible of this kind of effect.

The three ADEs 'edema of the ankle', 'extrasystoles' and 'falling hair' were considered as 'unrelated' or 'remote' to the treatment.

Conclusions

The results of this comparative clinical study, in double-blind condition versus placebo, confirm the progressive efficacy of chondroitin CS 4&6 on the subjective painful symptomology and on the articular mobility in patients suffering from knee osteoarthritis. Furthermore, it demonstrates that chondroitin sulfate CS 4&6 has the same activity whether it be administered in the form of an oral gel with 1200 mg taken once daily or in the form of 400 mg capsules taken three times per day.

The concomitant consumption of NSAIDs was one of the parameters analysed: it decreased significantly in subjects treated with chondroitin sulfate as compared to those receiving a placebo and resulting in an economical advantage for the treatment of arthrosic patients.

The tolerability of the two galenic forms of chondroitin sulfate studied and that of the placebo was very good.

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