Double-blind, dose-effect study of oral Chondroitin 4&6 Sulfate 1200 mg, 800 mg, 200 mg and placebo in the treatment of knee osteoarthritis

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Introduction

Osteoarthritis (OA) is the most common joint disorder, affecting approximately 12% of the population[5]. It is a typically age-related, heterogeneous syndrome, causing a lot of pain, functional disability and the necessity for surgical intervention.

The therapy of OA can be either non-pharmacological or pharmacological[4]. The treatment plan should in all cases be started with non-pharmacological methods such as education, change of regime, rehabilitation and the use of supportive devices like orthoses[9]. Should these be inadequate, pharmacological intervention should be introduced[11]. For symptomatic pain relief, local transdermal therapy, analgesics, opioids and intra-articular agents have been used.

According to the ACR classification, drugs used for the systemic therapy of OA can be structure-modifying or symptom-modifying[10]. The structure- (or disease-) modifying effect has not been proved for any drug so far. Symptom-modifying drugs are classified as rapid-acting (analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs]) and slow-acting, also called SYSADOA (symptomatic slow-acting drugs for OA). Chondroitin sulfate (CS) belongs to this class of new drugs, together with glucosaminsulfate, hyaluronic acid, diacer-

rhein, and the avocado-soya bean unsaponifiables. In spite of different chemical compositions and mechanisms of action which are probably not identical, these drugs share some similarities which distinguish them significantly from the NSAIDs, and therefore we can speak about a new class of drugs:

- the onset of symptomatic effect is delayed for 2–8 weeks,
- they typically possess a carry-over effect from 2–6 months,
- they alleviate pain and inflammation by a non-COX mechanism, so that typical gastrointestinal toxicity is not present and, generally speaking, the toxicity of these drugs is very low,
- these drugs are highly osteotropic and concentrate in joint cartilage,
- they have a potential structure-modifying effect.

Chondroitin sulfate has demonstrated typical SYSADOA characteristics in previous studies. It was tested in studies lasting from 2–12 months against a placebo and showed superiority in all trials in decreasing pain and also in improving function and quality of life[2,3]. UEBELHART has demonstrated possible structure-modifying effects in the retarding of knee OA[12] and VERBRUGGEN in the prevention of newly affected fingers in finger joint OA[13].

The optimal daily dose of CS had not as yet been established, as a dose-effect study was not available. We therefore decided to perform a short-term (three-month) dose-effect study with 200 mg, 800 mg and 1200 mg CS daily and a placebo.

Aims of the study

The objective of this study was to test the dose-effect of chondroitin sulfate at a dosage of 1200 mg *versus* 800 mg *versus* 200 mg *versus* placebo over a three-month treatment period in patients with femoro-tibial osteoarthritis.

Methodology

This was a phase III, randomised, double-blind, dose-effect study. Patients presenting with femoro-tibial OA were assigned to one of the four groups according to a randomisation key. The duration of the study was 90 days. Assessments of efficacy and tolerability were evaluated on days 0, 14, 42 and 90.

Medication

The different preparations of CS and the placebo were indistinguishable and packaged in identical sachets.

From day 0 to day 90 the patients were treated with one sachet daily of CS 1200 mg or CS 800 mg or CS 200 mg or placebo, in the evening, dissolved in 150 ml of water.

In addition, from day 0 to day 14 all patients were administered 3 × 50 mg diclofenac tablets per day.

Paracetamol was permitted as the rescue medication from day 15 onwards at a maximum dosage of 4 g/day. The exact quantity of paracetamol consumption was reported on the case report forms.

Other analgesics, nonsteroidal drugs, intra-articular steroids, as well as re-educational therapy, physiotherapy or alternative medicine (mesotherapy, acupuncture) were not permitted during the entire treatment period.

Efficacy evaluation
Primary efficacy criteria were LEQUESNE's Algofunctional Index of Knee OA – ISK[6] and spontaneous pain on HUSKISSON's Visual Analogue Scale (VAS) of 100 mm.

Secondary efficacy criteria were the global efficacy evaluation by the patients and by the physician using a 4-point scale (poor – fair – good – excellent) and paracetamol consumption from day 15 to day 90.

Tolerability evaluation
Judgement of tolerability was performed by the patients using a 4-point scale. Adverse drug reactions were registered according to GCP.

Patients
Inclusion criteria were:
1. femoro-tibial OA of the knee, according to the ACR criteria[1], with clinical symptoms having persisted for at least three months;
2. LEQUESNE's Index ≥ 8 points and pain on HUSKISSON's VAS ≥ 40 mm (pain during daily physical activity);
3. persistence of some articular joint space documented with a radiography;
4. age over 30 years.

Exclusion criteria were:
1. isolated patello-femoral OA (or predominant);
2. genu varum or valgum > 8°;
3. surgery of the knee in the six months preceding the start of the study;
4. secondary OA (arthritis, metabolic arthropathy, PAGET's disease);
5. SYSADOA in the last three months;
6. intra-articular steroids during the last month.

Statistical evaluation
Age, weight, height and laboratory parameters were analysed according to a one-way Analysis of Variance (AOV) and multiple comparisons between groups (Least Significant Difference) were calculated.

Sex, pain location, adverse drug reactions and drop-outs were analysed to χ^2 contingency tables.

Consumption of paracetamol was analysed by the KRUSKALL-WALLIS test. The variables VAS and LEQUESNE's Index were analysed by AOV with repeated measures and multiple comparisons between groups (Least Significant Difference) and were calculated with the intention-to-treat (ITT) analysis. Judgements of efficacy and tolerability treatments, expressed by the physician and the patient, were analysed according to the linear trend test.

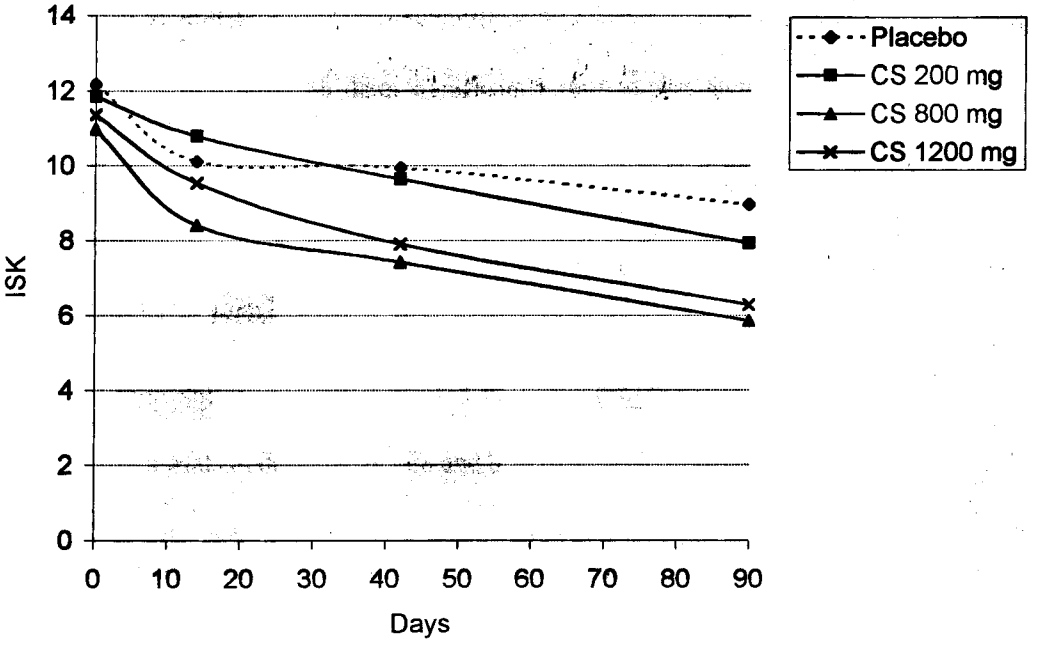

Figure 1
LEQUESNE's Index

The Area Under the Curve (AUC) was calculated according to time recording (day 0, day 14, day 42, day 90) as an abscissa for VAS and ISK. This parameter, after transformation as the square root, was analysed by an analysis of covariance (ANCOVA) using basal values as covariates.

Results

The patients' characteristics are reported in *Table I.* Altogether 140 patients were recruited and randomly divided into four groups of 35 patients each. There were 36 males (26%) and 104 females (74%). The mean age of the whole patient population was 64.9 ± 10.7 years, mean duration of symptoms was 4.1 ± 4.7 years, mean LEQUESNE's Index at baseline was 11.59 ± 2.36 points and mean pain on VAS was 70.0 ± 11.0 mm. The four groups were statistically homogeneous for purposes of comparison.

LEQUESNE's Index (ISK)
The functional status of the patients in their daily lives was evaluated using LEQUESNE's Index.

Table I
Patients' characteristics at entry (means ± SD)

Group	Placebo (n = 35)	CS 200 mg (n = 35)	CS 800 mg (n = 35)	CS 1200 mg (n = 35)	p between groups
Sex (M/F)	5/30	14/21	8/27	9/26	n.s.
Age (years)	67.1 ± 10.4	62.6 ± 11.6	63.9 ± 9.8	65.9 ± 10.6	n.s.
Weight (kg)	73.1 ± 12.4	72.8 ± 11.2	76.4 ± 14.2	75.2 ± 15.6	n.s.
Symptomatic for x years	3.7 ± 3.9	5.0 ± 6.0	3.7 ± 3.8	3.9 ± 5.1	n.s.
LEQUESNE's Index	12.2 ± 2.6	11.8 ± 2.3	11.3 ± 2.3	11.0 ± 2.1	n.s.
VAS (mm)	71.0 ± 11.1	70.3 ± 12.7	68.7 ± 9.5	69.9 ± 10.8	n.s.

CS = chondroitin sulfate; VAS = Visual Analogue Scale.

Table IIa
LEQUESNE's Index (means ± SD)
AOV with repeated measures and multiple comparisons (Least Significant Difference)

	Placebo	CS 200 mg	CS 800 mg	CS 1200 mg
Basal	12.17 ± 2.57	11.84 ± 2.34	10.97 ± 2.04	11.36 ± 2.38
Day 14	10.11 ± 3.06	10.79 ± 3.01	8.40 ± 2.22	9.53 ± 2.63
Day 42	9.94 ± 2.45	9.64 ± 2.99	7.41 ± 2.33	7.90 ± 3.12
Day 90	8.97 ± 3.28	7.93 ± 2.98	5.86 ± 3.34	6.29 ± 2.75

CS = chondroitin sulfate; AOV = Analysis of Variance.

Table IIb
Delta variations on LEQUESNE's Index
AOV: multiple comparisons between groups

Placebo	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 200 mg	1.00	0.0810	0.03	0.9602	–0.71	0.2122
	CS 800 mg	0.29	0.6175	–0.83	0.1466	–1.93	0.0008
	CS 1200 mg	–0.57	0.3181	–1.73	0.0027	–1.86	0.0013
CS 200 mg	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 800 mg	–0.71	0.2122	–0.86	0.1333	–1.21	0.0343
	CS 1200 mg	–1.57	0.0062	–1.76	0.0023	–1.14	0.0463
CS 800 mg	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 1200 mg	–0.86	0.1346	–0.90	0.1174	0.07	0.9006

CS = chondroitin sulfate; AOV = Analysis of Variance.

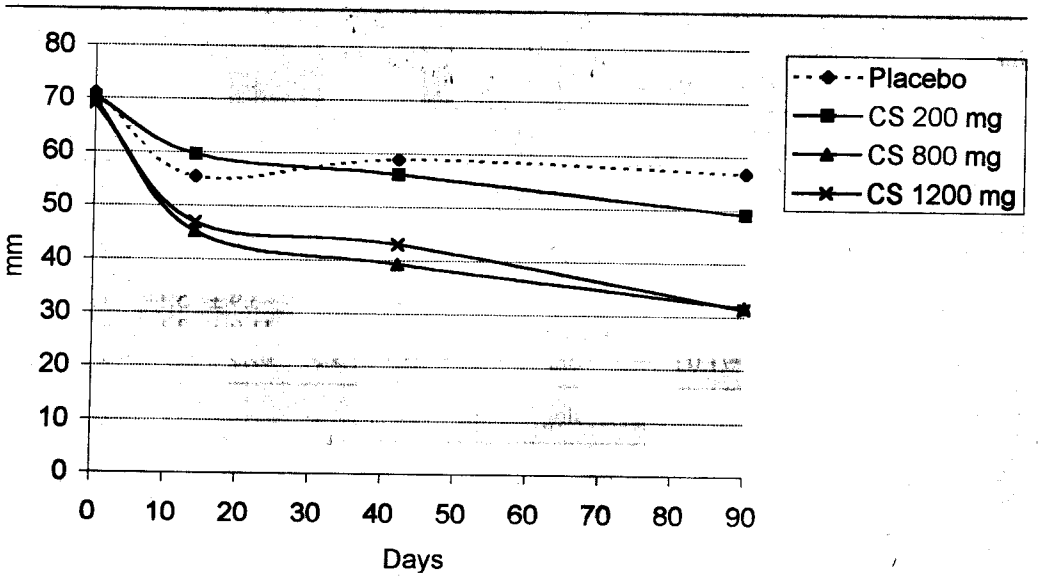

Figure 2
Pain on HUSKISSON's VAS

For this parameter, a decrease in mean values was statistically highly relevant within each treatment group from day 14 onwards (AOV within each group: $p < 0.001$) (*Fig. 1* and *Tab. IIa*).

Table IIb reports the statistical results of the multiple comparisons between groups calculated with the AOV on LEQUESNE's Index.

The doses CS 1200 mg and CS 800 mg were significantly more effective than the placebo and than the dose CS 200 mg. The results were evident from day 42 for CS 1200 mg, whereas for dose CS 800 mg the results were only evident at day 90. AUC values obtained for ISK in the different groups confirmed that there was no difference between CS 200 mg and the placebo (p = n.s.), that the doses of CS 800 mg and CS 1200 mg were significantly more effective than CS 200 mg and the placebo ($p < 0.01$) and that there was no difference between CS 800 mg and CS 1200 mg (p = n.s.).

Pain on the Visual Analogue Scale

Basically, these results reflected those obtained for the LEQUESNE's Index. Knee joint pain evaluated with HUSKISSON's VAS decreased in a statistically significant manner within each treatment group from day 14 onwards (AOV within each group: $p < 0.001$) (*Fig. 2* and *Tab. IIIa*). *Table IIIb* summarises the statistical results of the multiple comparisons between groups calculated with the AOV on the VAS. On day 14, there was only a statistical difference between the placebo and the highest CS dose (CS 1200 mg). At this control visit, the groups treated with CS 800 mg and CS 1200 mg did not differ between themselves but their pharmacological effect was statistically different as compared to the lowest dose (CS 200 mg). The dose of CS 200 mg did not achieve a statistically different result when

Table IIIa
Pain on HUSKISSONS's VAS (mm) (means ± SD)

	Placebo	CS 200 mg	CS 800 mg	CS 1200 mg
Basal	71.0 ± 11.1	70.3 ± 12.7	69.6 ± 9.6	69.0 ± 10.8
Day 14	55.5 ± 16.1	59.6 ± 17.8	45.2 ± 15.8	46.9 ± 21.5
Day 42	58.9 ± 16.4	56.1 ± 18.7	39.2 ± 15.8	43.0 ± 19.8
Day 90	56.8 ± 21.8	49.1 ± 17.8	31.7 ± 18.1	31.4 ± 19.2

CS = chondroitin sulfate; VAS = Visual Analogue Scale.

Table IIIb
Delta variations on VAS
AOV: multiple comparisons between groups

Placebo	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 200 mg	4.77	0.2485	− 2.03	0.6234	− 7.00	0.0907
	CS 800 mg	− 4.43	0.2841	−10.40	0.0121	−21.83	0.0000
	CS 1200 mg	−11.09	0.0075	−21.71	0.0000	−25.31	0.0000
CS 200 mg	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 800 mg	− 9.20	0.0264	− 8.37	0.0432	−14.83	0.0004
	CS 1200 mg	−15.86	0.0001	−19.69	0.0000	−18.31	0.0000
CS 800 mg	***vs***	**Delta 14 day**	***p***	**Delta 42 day**	***p***	**Delta 90 day**	***p***
	CS 1200 mg	− 6.66	0.1076	−11.31	0.0064	− 3.49	0.3990

CS = chondroitin sulfate; VAS = Visual Analogue Scale; AOV = Analysis of Variance.

Table IV
Efficacy evaluation by both patients and physician
(percentage of good/excellent judgements in study groups)

Treatment groups	**Day 14**		**Day 42**		**Day 90**	
	Patient	**Physician**	**Patient**	**Physician**	**Patient**	**Physician**
Placebo	42.9	40.0	17.1	20.0	31.4	40.0
CS 200 mg	31.4	31.4	34.3	37.1	48.6	51.4
CS 800 mg	54.3	48.6	62.9	65.7	82.9	77.1
CS 1200 mg	60.0	54.3	68.6	65.7	68.6	74.3
***p* between treatment groups**	0.0490	0.1094	0.0000	0.0000	0.0001	0.0005

CS = chondroitin sulfate

compared with the placebo both on day 42 and on day 90. On the contrary, CS 800 mg and CS 1200 mg both showed a statistically significant difference to the placebo group and to the CS 200 mg group at day 42 and maintained this difference also at day 90. CS 1200 mg was more effective than CS 800 mg at day 42, but there was no difference between them at the end of the study (day 90).

The overall analgesic effect expressed in terms of the AUC of the pain scores (VAS) was also analysed by means of the ANCOVA and the results are similar to those obtained for ISK. There was no significant difference between CS 200 mg and the placebo (p = n.s.). The doses CS 800 mg and CS 1200 mg were significantly more effective than the placebo ($p < 0.01$) and more effective also than CS 200 mg ($p < 0.01$). There was no difference between CS 800 mg and 1200 mg (p = n.s.).

Efficacy evaluation

On day 14, no statistically significant difference was found between the four treatment groups, if we consider the percentage of efficacy judgements reported as good/excellent by the patients. The difference in percentage became statistically significant from day 42 onwards, allowing us to conclude that the patients receiving the two highest doses of CS were those most satisfied with their treatment *(Tab. IV).*

Paracetamol consumption

The paracetamol consumption which occurred from day 15 to day 90 was reported for every patient. Results were expressed as the mean total number of tablets. Statistically there was no difference between CS 200 mg (53.6 ± 59.3) and the placebo (69.6 ± 68.6). Consumption was statistically lower in the groups CS 800 mg (31.6 ± 49.5) and CS 1200 mg (38.0 ± 49.6) than in the placebo and in the CS 200 mg groups ($p < 0.01$).

Assessment of tolerability

The overall tolerability judgement, expressed by both the physician and the patients, was reported as good/excellent in most of the cases (p = n.s.).

Adverse events

Concerning adverse events there was no difference between the CS treatment groups and the placebo group. One patient in the CS 200 mg group complained of slight epigastralgia on day 42, whereas three patients in the placebo group reported mild nausea, stomach ache or difficult digestion.

Drop-outs

There were three premature withdrawals from the study in total (1 placebo, 1 CS 200 mg and 1 CS 1200 mg) and no statistical difference was found between the study groups.

Laboratory assessment of safety

We observed no difference in laboratory safety parameters between and within the four study groups.

Discussion

This study confirmed that CS was significantly more effective in the suppression of pain and in improving function as compared with the placebo. This effect was delayed; in fact, the difference only became evident starting from the control visit on day 42. The effect was dose-related, as doses of CS 800 mg and CS 1200 mg were more effective than CS 200 mg, but there was no significant difference between CS 800 mg and CS 1200 mg daily. Only on day 14 was CS 1200 mg more effective than CS 800 mg. Based on the results of our study we can recommend the following treatment: CS 1200 mg for the first two weeks, followed by CS 800 mg daily. As had been shown earlier[2], there was no difference between the single daily dose of CS 1200 mg and the dose of 3×400 mg CS/day. Therefore, taking into account patient compliance, the monodose seems to be the best choice.

A basic question concerning the treatment of OA is what should we treat first: structure or symptoms or both? We believe that symptom modification is the most important option and that all potential OA drugs should primarily be symptom-modifying, for reasons of ethics, patient acceptance and, possibly, more rapid regulatory approval. A potential structure-modifying effect should only be considered as a second step in clinical drug development programmes. Furthermore, the natural progression of OA is very slow[7,8] so that it is not clear whether currently available plain radiographs are able to differentiate between treatment groups (even after standardisation); possibly some other techniques (MRI) or invasive methods have to be implemented in clinical trials with potential disease-modifying anti-osteoarthritis drugs.

In conclusion, CS is a drug with typical SYSADOA activity and with some evidence of structure modification[1,6]. It is practically non-toxic and should be recommended for the long-term treatment of OA.

Summary

A prospective, randomised, double-blind, dose-effect study was performed comparing four different doses of chondroitin sulfate (CS 1200 mg, 800 mg, 200 mg daily) with a placebo in the treatment of femoro-tibial osteoarthritis over a treatment period of three months. A total of 140 patients were recruited in three different centres: one centre in the Czech Republic, one in Italy and one in Hungary. The study demonstrated the significant superiority of the two higher doses of CS, namely 800 mg and 1200 mg, as compared to placebo treatment and to the lower dose of CS 200 mg. This difference became evident starting from day 42 and was maintained until the end of the study (day 90). CS 200 mg was not more effective than the placebo. No difference was found between CS 800 mg and CS 1200 mg.

In conclusion, CS 1200 mg/day for the first two weeks, followed by CS 800 mg/day could be recommended as a therapeutic scheme.