EXTENDED REPORT

Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study

Bernard Mazières, Michel Hucher, Mohammed Zaïm, Patrick Garnero

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Objective: To evaluate the efficacy and tolerability of chondroitin sulphate (chondroitin sulphate) in knee osteoarthritis.

Patients and methods: A 24-week, randomised placebo-controlled trial of chondroitin sulphate (1 g/day) in patients with symptomatic knee osteoarthritis as measured on a visual analogue scale. Pain on daily activities and Lequesne's Index were the primary efficacy criteria. Secondary outcomes included the rate of responders according to the outcome measures in rheumatoid arthritis clinical trials of the Osteoarthritis Research Society International (OMERACT-OARSI) criteria, quality of life, patient's/physician's global assessments and carry-over effect after treatment. Biochemical markers of bone (CTX-I), cartilage (CTX-II) and synovium (hyaluronic acid) metabolism were also measured. Safety was assessed by recording adverse events (AEs). Statistical analysis was performed on the inter-group differences in the intention-to-treat population.

Results: 307 patients were included in the study. 28 (9%) patients discontinued the study because of lack of efficacy or AEs. At the end of treatment, the decrease in pain was -26.2 (24.9) and -19.9 (23.5) mm and improved function was -2.4 (3.4) (-25%) and -1.7 (3.3) (-17%) in the chondroitin sulphate and placebo groups, respectively ($p=0.029$ and 0.109). The OMERACT-OARSI responder rate was 68% in the chondroitin sulphate and 56% in the placebo group ($p=0.03$). The investigator's assessments and short form 12 (SF-12) physical component reported improvement more frequently in the chondroitin sulphate than in the placebo group ($p=0.044$ and 0.021 , respectively). No significant difference was observed between treatment groups for changes in biomarkers over 24 weeks. However, there was a significant difference between non-responders and responders according to the OARSI criteria for 24-week changes of CTX-I ($p=0.018$) and CTX-II ($p=0.014$). Tolerance was considered to be satisfactory.

Conclusion: This study failed to show an efficacy of chondroitin sulphate on the two primary criteria considered together, although chondroitin sulphate was slightly more effective than placebo on pain, OMERACT-OARSI response rate, investigator's assessment and quality of life.

See end of article for authors' affiliations

Correspondence to: Professor B Mazières, Department of Rheumatology, Rangueil University Hospital, Avenue Jean-Poulhes, 31059 Toulouse Cedex 9, France; mazières@cict.fr

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Osteoarthritis (OA) is the most common form of arthritis, affecting the knees in 30% of people aged ≥ 65 years.¹ Although only about 50% of them have signs and symptoms, the number of adults clinically affected is considerable and is increasing with the increasing average age of populations.

Current treatments for OA include pharmacological and non-pharmacological treatment.^{2–3} The European League Against Rheumatism (EULAR) recommendations also include the so-called "symptomatic slow-acting drugs for treating osteoarthritis" (SYSADOA) in the 10 final suggestions for management of the disease.²

The need to define new classes of drugs for treating OA was an emerging concept in France in the early 1990s and attempts have been made to correctly classify old drugs whose assessment was poor.⁴ In 1992, a French annual meeting including representatives of the Faculty, the registration authorities and the pharmaceutical industry addressed the question of classification of the "anti-arthritic drugs". The concept of SYSADOA was proposed,⁵ officially presented in the *French Journal of Rheumatology*⁶ and then adopted at the international level.⁷ This therapeutic class includes chondroitin and glucosamine sulphates, diacerein, avocado-soybean extracts and hyaluronic acid (the latter delivered by an intra-articular route). All these drugs have been evaluated in randomised controlled trials. However, the efficacy of this class of treatment is still debated.^{8–13} Chondroitin sulphate is a glycoaminoglycan that is a component

of the aggrecan structure that makes up the articular cartilage. It binds collagen fibrils and limits water content by cooperating with hyaluronan. It plays a role in allowing the cartilage to resist tensile stresses during loading conditions. Exogenous administration of chondroitin sulphate has an anti-inflammatory activity probably through a free radical-scavenging effect and chondroitin sulphate in vitro competitively inhibits the degradative enzymes of the cartilage. It increases the in vitro production of proteoglycans and counteracts the negative effect of interleukin 1 β (IL1 β).¹⁴ In humans, chondroitin sulphate has been studied in several clinical trials and reviewed in meta-analyses.^{8–9} However, because both methodological quality and efficacy vary widely from one study to another, the reliability of these meta-analyses is questionable¹¹ and additional randomised placebo-controlled trials are clearly warranted.

The primary objective of our study was thus to assess the clinical efficacy of chondroitin sulphate in a 6 month

Abbreviations: AE, adverse event; ATP, according to protocol; CTX-II, crosslinked C-telopeptide of type II collagen; CRP, case report form; CVs, coefficients of variation; ITT, intention to treat; JSN, joint space narrowing; LOCF, latest observation carried forward; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International; OMERACT, outcome measures in rheumatoid arthritis clinical trials; S-CTX-I, serum crosslinked C-telopeptide of type I collagen; SF-12, short form 12; SYSADOA, symptomatic slow-acting drugs for treating osteoarthritis; U-CTX-I, urinary crosslinked C-telopeptide of type I collagen; VAS, visual analogue scale

randomised placebo-controlled trial of patients with symptomatic knee OA using an approved drug (Structum, 500 mg (Pierre Fabre Company, La Chartreuse, France)). Because of the short-term duration of the trial, radiological progression could not be reliably assessed. Consequently, we also investigated the effects of chondroitin sulphate on biological markers of joint tissue metabolism, which have been shown to be predictive of radiological progression in knee OA and hip OA.^{15 16}

PATIENTS AND METHODS

Study design

This prospective, randomised, double-blind, placebo-controlled, multicentre clinical trial was carried out by 99 rheumatologists trained for clinical trials, in France and Switzerland, from October 2003 to March 2005. The study was approved by independent ethics committees and conducted according to the Declaration of Helsinki and European good clinical practice guidelines. Patients gave written informed consent before their inclusion. A validation committee was set up to verify that the trial was properly conducted and that the review at completion was performed under strict blind conditions. The overall design of the study consisted of a 24-week treatment period followed by an 8-week post-treatment follow-up. After the inclusion visit, the patients were examined four times (fig 1).

Study objectives

The primary objective was to assess the clinical efficacy of chondroitin sulphate on pain and function in the treatment of symptomatic medial knee OA. The secondary objectives were to assess the rate of responders according to the outcome measures of the rheumatoid arthritis clinical trials of the Osteoarthritis Research Society International (OMERACT-OARSI) criteria,¹⁷ to evaluate the carry-over effect 8 weeks after the end of the treatment and to obtain information on the safety of chondroitin sulphate as compared with placebo.

Patients

Outpatients of both sexes, aged 50–80 years, with medial knee OA, defined according to American College of Rheumatology criteria¹⁸ were included.

To be eligible, patients had to present with symptomatic knee OA that had lasted for >6 months, with pain during daily activity ≥ 40 mm on a 0–100 mm visual analogue scale (VAS),¹⁹ a Lequesne's Index Score²⁰ of between 6 and 12 and to fall into stages 2/3 of the Kellgren and Lawrence (K/L) classification²¹ on an anterior–posterior view in an extended standing position taken within the previous 6 months. In case of bilateral

involvement, the most painful knee at entry was selected as the target joint and was used throughout the study.

We excluded from the study patients with secondary knee OA,¹⁸ isolated patello-femoral OA and those requiring knee surgery in the coming year. Subjects with known hypersensitivity or allergy to chondroitin sulphate or paracetamol were not included. We also excluded patients who had used non-steroidal anti-inflammatory drugs (NSAIDs) for >50% of the time during the 2 months before inclusion. Patients who had used NSAIDs within 48 hours before inclusion or SYSADOA, steroid by any route, intra-articular hyaluronic acid or arthroscopic debridement within 6 months before inclusion were not randomised. Also, patients with other active or severe diseases were excluded.

Randomisation, drug administration and concomitant treatments

Patients were randomised to receive a hard capsule of either 500 mg of chondroitin sulphate or placebo, twice daily by oral route. This dose was selected because it was within the 800 mg to 2 g range used in previous studies¹¹ and it was the officially recommended dose (summary of product characteristics (SmPC)). The patients were assigned to one of the two groups according to a pre-established computer-generated global randomisation list (treatment number), with balanced blocks of four treatments. The two drugs were not distinguishable from each other.

If necessary, patients were authorised to take rescue drugs, starting with paracetamol (up to 4 g/day). Patients were asked to bring back all the boxes at the next visit for accountability. In cases where paracetamol treatment proved to be insufficient, NSAIDs allowed.

Drugs prescribed for a disorder other than OA were authorised and reported in the case report form (CRF). All SYSADOA, opioids or steroids by any route of administration, topical drugs or any physical therapy applied to the painful knee were forbidden during the trial. The patient recorded exact consumption in a self-report diary. The rescue drugs were forbidden before each evaluation visit: NSAIDs in the 2 days and paracetamol in the 12 h before the visit.

Compliance was assessed by asking the patient at each visit if he/she had regularly taken the treatment and by an accurate count of empty and returned boxes in the CRF. Compliance was considered as acceptable if $\geq 80\%$.

Outcome measures

As advised by the latest European Agency for the Evaluation of Medicinal Products (EMA) recommendations,²² the following end points were used as primary outcome measurements:

- Mean variation of pain on activity at the end of the 24 weeks of treatment compared with the score at inclusion, using a 0–100 mm VAS.
- Mean variation of Lequesne's Index Score at the end of the 24 weeks compared with the score at inclusion. This index consists of a 10-item investigator-administered questionnaire, which allows patients to rate pain or discomfort, stiffness, difficulty performing daily activities and their maximum walking capacity. The total score varies from 0 (no functional consequence) to 24 (major disability).

Secondary outcome measurements included: (1) percentage of responders according to the OMERACT-OARSI definition after 24 weeks of treatment; (2) change in spontaneous pain at rest (VAS); (3) global patient's and investigator's assessments of clinical improvement using a 7-point scale from +3 (much better) to –3 (much worse) (4) the consumption of analgesics and NSAIDs; (5) quality-of-life assessment on physical and

Figure 1 Schedule of the trial. After a 1-week screening period, the patients were randomly placed either in the chondroitin sulphate group (500 mg twice daily) or in the placebo group for 24 weeks, and then entered the 8-week follow-up period. Bid, twice daily.

mental component scores on the SF-12; and (6) changes in pain on activity (VAS) and Lequesne's Index score at the end of the follow-up period compared with the end-of-treatment visit.

Exploratory outcome measurements included Radiological variables of OA

Radiographs were read centrally (BM) and the K/L score was determined. For each knee, osteophyte size was graded from 0 (no osteophyte) to 3 (large osteophyte) at four different sites (lateral/medial condyles and tibial plateaux). The degree of joint space narrowing (JSN) of the tibiofemoral compartment was graded 0 (absent), 1 (<25% reduction of the inter-bone distance), 2 (25–50% reduction), 3 (>50%) or 4 (bone to bone), a modified grade scale assessed in the literature.²³ Cumulative scores were calculated for total osteophytes by adding the individual osteophyte scores of both knees for each subject (ranges 0–24) and for total JSN score by summing the individual JSN (ranges 0–8). Following Goldberg *et al.*²⁴ we also calculated an articular OA index based on the total amount of cartilage in the joints involved (from knee, hip, hand and spine; table 1).

Biochemical markers

Fasting serum and second morning void urine were collected at baseline and 24 weeks and stored at –70°C until analysed. Subjects were asked to perform their usual routine activity and to fast until collection of blood and urine, which took place between 07:30 and 10:00.

Serum C-terminal crosslinked telopeptide of type I collagen (S-CTX-I), a marker of bone resorption, was measured on the Elecsys 2010 automate analyser (Roche Diagnostics, Mannheim, Germany). Intra-assay and interassay coefficients of variation (CVs) were below 6%.²⁵ Urinary C-terminal cross-linked telopeptide of type II collagen (CTX-II), a marker reflecting degradation of articular cartilage, was measured by ELISA (Cartilaps, Nordic Bioscience, Herlev, Denmark).²⁶ Intra-assay and interassay CVs were lower than 8% and 15%, respectively. Measurements were corrected for urinary creati-

nine (Cr) measured by a standard colorimetric assay. Serum hyaluronic acid (S-HA), an index of synovial tissue metabolism, was measured by ELISA (Hyaluronic Acid Test kit, Corgenix, California, USA). Intra-assay and interassays CVs were lower than 6% and 9%, respectively.

Assays were performed in duplicate with both baseline and 24-week samples from each individual in the same assay. Measurements were performed centrally, blinded to treatment.

Safety was assessed by recording AEs spontaneously reported by the patients on request at each visit. AEs were analysed with regard to their number, seriousness, intensity and causal relationship with treatment and outcome. AEs were collected up to 8 weeks after the end of the treatment.

Statistical analyses

The sample size was calculated based on the primary outcome measurement of change in global pain during activity, with an expected mean inter-group difference of 10 mm on VAS, a standard deviation of the mean distribution of 25 mm, a bilateral α risk of 5% and a power of 90%. With a predicted withdrawal rate of 12%, the estimated necessary sample size was 150 patients in each group. The same calculation was performed on the Lequesne's Index (with an inter-group difference of 2, and a SD of 3) and gave a smaller number of patients. Thus, 300 patients was the number finally chosen.

Demographic and baseline data were compared within the two groups, using a Student's *t* test for quantitative variables and χ^2 test for qualitative variables.

Changes in variables at each visit were compared between treatment groups by an analysis of covariance using baseline values as a covariate for quantitative variables, a χ^2 test or Fisher's exact test for nominal variables and a Mann-Whitney *U* test for ordinal variables. The principal analysis of efficacy was made on the intention-to-treat (ITT) population, which comprised all randomised patients who had received at least one capsule and who were evaluated at least once during the trial, using the last observation carried forward (LOCF) method as the end point in cases of missing data or premature discontinuation. A secondary analysis was performed on the according-to-protocol (ATP) population, which comprised the patients who fulfilled the protocol requirements without any major deviation, as determined by the validation committee at the blind review.

The main analysis was performed on the two main outcome measures (pain and function) separately. The variable analysed was the variation between inclusion and week 24 or LOCF. Efficacy was judged on a significantly better result in the chondroitin sulphate group as compared with placebo on both criteria. Therefore adjustment for multiplicity was not necessary.

Association between biochemical marker levels and clinical and radiological parameters of OA at baseline was assessed by linear or logistic regression on log-transformed data, after adjustment for age, sex and body mass index. Differences of radiological variables per quartile of markers were analysed by analysis of variance (ANOVA), including age, sex and body mass index as covariates. Safety analysis was performed on the ITT population.

The statistical analysis was performed using SAS software V.8.2. All statistical tests were carried out two tailed at the 5% level of significance.

RESULTS

Population

Three hundred and twenty-two patients were screened. The available ITT population contained 307 patients (153 chondroitin sulphate; 154 placebo). During the 24 weeks of the

Table 1 Baseline demographic and clinical characteristics of the patients in the intent-to-treat efficacy population (n = 307)

Parameters	Chondroitin sulphate (n = 153)	Placebo (n = 154)
Age (years)	66 (8.8)	66 (7.7)
Sex (% females)	71	69
Body mass index (kg/m ²)	28.8 (5.1)	28.8 (5.2)
Reported familial history of knee OA (%)	40	46
History of trauma* or meniscectomy (%)	16	15
Hand/hip/spine OA† (%)	41/13/73	40/10/69
Duration of disease (years)	6.2 (6.8)	6.6 (7.6)
Pain during activity (VAS; mm)	62 (13)	61 (12)
Pain at rest (VAS; mm)	40 (20)	40 (22)
Lequesne's Index	9.5 (2)	9.4 (2)
Kellgren-Lawrence stages 2–3 (%)	69	59
S-CTX-I (ng/ml)	0.44 (0.27)	0.39 (0.22)
U-CTX-II (ng/mmol Cr)	389 (247)	375 (238)
S-HA (ng/ml)	86 (71)	79 (61)

OA, osteoarthritis; S-CTX-I, serum crosslinked C-telopeptide of type I collagen; S-HA, serum hyaluronic acid; U-CTX-II, urinary crosslinked C-telopeptide of type II collagen VAS, visual analogue scale.
Data expressed as mean (SD) unless stated otherwise.

*Trauma included joint fracture, sprain and contusion.

†Hip/spine osteoarthritis (OA) were defined on x rays if the patients could provide radiographs of these areas, with signs of OA. Hand OA was defined on examination by the physician.

treatment period, 28 (9%) patients withdrew; 14 in each group (fig 2). After excluding the 85 major deviations (including premature discontinuations), 111 patients remained in each group for the per protocol population. The two main violation deviations were radiographic staging failures (36%) and missing data or too short exposure to treatment (ie, <150 days; 34%). The mean study duration was 215 (49) days (ITT population).

Demographic characteristics, OA history and clinical, radiographic and biological status at baseline were similar in the two groups (table 1). More than 92% of the patients were compliant (mean compliance: 96%, 16).

Efficacy

Primary end points

Table 2 shows the changes in pain during daily activity and in the Lequesne's Index in patients treated with chondroitin sulphate and placebo.

The change from baseline to week 24 of the pain during daily activity was -26.2 (024.9) mm (-41%) and -19.9 (23.5) mm (-32%) in the chondroitin sulphate and placebo groups, respectively ($p = 0.029$), resulting in an inter-group difference of 6.3 mm in favour of chondroitin sulphate. The change from baseline to week 24 of the Lequesne's Index was -2.4 (3.4) (25%) in chondroitin sulphate and -1.7 (3.3) (-17%) in placebo ($p = 0.109$).

Secondary end points

Table 3 shows the results of the secondary end points in the chondroitin sulphate and placebo groups.

Figure 2 Flowchart of patients included in the study.

The main difference between groups was observed for the number of OMERACT-OARSI responders: 68% (104/153) of patients in the chondroitin sulphate group, compared with 56% (86/154) in the placebo group ($p = 0.03$). Pain at rest, from inclusion to week 24, decreased by 19 (24) mm and 17 (24) mm in the chondroitin sulphate and placebo groups, respectively (NS).

Regarding the global evaluation, the difference between groups was almost statistically significant for the patients' ($p = 0.085$) and for the investigator's ($p = 0.044$) assessment.

The SF-12 physical component was significantly improved in the chondroitin sulphate group compared with the placebo group after 6 months of treatment ($p = 0.021$).

The duration of paracetamol use was similar in patients taking chondroitin sulphate and placebo. Most patients (86.6%) used NSAIDs on <10% of the study days without any inter-group difference.

Regarding carry-over effects, there was a slight but not significant decrease between weeks 24 and 32 in pain intensity during activity. There was no worsening of the Lequesne's Index, and pain at rest remained improved.

The analyses for the per protocol population supported results obtained in ITT patients. In particular, the change from baseline to week 24 of the pain during daily activity was -27.3 (24.4) mm (-43%) and -20.8 (23.0) mm (-34%) in chondroitin sulphate and placebo groups, respectively ($p = 0.05$). The change from baseline to week 24 of the Lequesne's Index was -2.2 (3.2) (-23%) in chondroitin sulphate and -1.7 (3.2) (-18%) in placebo.

Biochemical markers of joint tissue turnover

Table 4 shows mean levels of biochemical markers of joint tissue turnover. Baseline and week 24 samples were available for the measurements of biomarkers in 270 individuals for serum and in 267 individuals for urine specimens. At baseline, CTX-II correlated significantly with K/L grade ($r = 0.24$, $p < 0.001$), the cumulative scores of osteophytes ($r = 0.30$, $p < 0.0001$) and of JSN ($r = 0.23$, $p < 0.001$). HA also correlated significantly with the osteophyte score ($r = 0.21$, $p = 0.0002$) and slightly with higher K/L grades ($r = 0.13$, $p = 0.051$) and the score of JSN ($r = 0.12$, $p = 0.064$). There was no significant association between CTX-I and radiological features of OA.

There was no significant difference between groups in the 24-week changes of urinary CTX-II, serum CTX-I and S-HA (table 4). When the analysis was restricted to patients with baseline levels above the median, similar findings were observed (data not shown).

Because there was no difference between the chondroitin sulphate and placebo groups on changes in the biochemical markers, we combined these two groups to analyse their relationship with clinical response. CTX-I and CTX-II increased significantly but modestly over 24 weeks in non-responders according to the OMERACT-OARSI criteria, but did not change in responders (mean (SD) change over 24 months: 0.03 (0.13) vs -0.01 (0.15) ng/ml, $p = 0.018$ for CTX-I and 61 (266) vs -17 (167), $p = 0.014$ for CTX-II in non-responders and responders, respectively).

Safety

The safety population included 309 patients (received the treatment of at least one dose, were not assessable for efficacy but were included in the safety analysis). Seventy-five patients (49%) in the chondroitin sulphate group and 76 (49%) in the placebo group reported at least one treatment-emergent adverse event. The treatment was prematurely discontinued because of AEs for 13 patients in the chondroitin sulphate group and 8 patients in the placebo group (table 5). A total of

Table 2 Changes in pain during daily activity and in the Lequesne's Index in patients treated with chondroitin sulphate and placebo.

Parameters	Groups	Week 0	Week 4	Week 12	Week 24	Week 32
Pain during activity (VAS; mm)	Chondroitin sulphate	61 (13)	48 (21)	40 (23)	36 (24)	33 (23)
	Placebo	61 (13)	51 (20)	42 (21)	41 (23)	40 (24)
Lequesne's Index	Chondroitin sulphate	9.5 (2.1)	8.3 (2.8)	7.8 (3.6)	7.2 (3.7)	6.8 (3.9)
	Placebo	9.4 (1.8)	8.4 (2.4)	7.9 (3.1)	7.7 (3.3)	7.5 (3.6)

VAS, visual analogue scale.

The two primary efficacy criteria were the difference of changes from baseline at week 24 between the two groups.

Data are expressed as mean (SD).

18 AEs possibly or probably related to treatment in 14 patients in the chondroitin sulphate group and 20 in 16 patients in the placebo group were reported. In both treatment groups, the majority (50%) of these AEs were related to gastro-intestinal troubles including dyspepsia, nausea, vomiting, abdominal pain and diarrhoea.

DISCUSSION

In accordance with the EMEA recommendations,²² both pain and function were selected as primary criteria. In this study, pain during daily activity was significantly more reduced in the chondroitin sulphate group than in the placebo group, but the inter-group difference was small (6.3 mm on VAS) and its clinical relevance is questionable. Changes in function were not different between groups. Because the value of Lequesne's Index at baseline was moderately increased, this may have limited the power of the study to detect a significant change of this parameter, although the value was similar to that reported in previous trials using this index as an efficacy outcome.

Secondary end points showed some discrepancies according to the parameters considered. Several of them were not different between the two groups (analgesic and NSAID consumption, pain at rest, global evaluation by the patient and carry-over effect), but the OMERACT-OARSI responder rate was higher in the chondroitin sulphate treatment group

(68%) than in the placebo group (56%). The global assessment by the investigators and the SF-12 physical component improvement were also significantly better in the chondroitin sulphate group.

It is rather difficult to make a clear appraisal of the efficacy of chondroitin sulphate through the literature, despite several meta-analyses or reviews.⁸⁻¹¹ It appears that the higher the methodological quality used in these trials, the lower the effect of chondroitin sulphate observed. In a review including seven randomised controlled trials,¹¹ the pooled effect size on pain during activity was 0.6 (95% CI 0.26 to 0.94), with a mean difference of pain on VAS between groups of 11.7 mm at 3 months and of 25 mm at 6 months of treatment in favour of chondroitin sulphate. The pooled effect size of function (measured on Lequesne's Index) was 0.57 (95% CI 0.26 to 0.88), with mean inter-group differences of the index of 2 at 3 months. Recently, the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)¹² failed to demonstrate any significant effect of glucosamine hydrochloride or chondroitin sulphate alone on the symptoms of knee OA, although the combined treatment was effective in the subgroup of patients with moderate-to-severe pain at baseline. In this trial, the effect sizes were 0.26 for pain and 0.21 for function (Lequesne's Index). These values are closed to the lower limit of the small effect range (0.2-0.4). Thus, overall, this randomised controlled trial failed to demonstrate a substantial superiority of chondroitin sulphate over placebo as defined by these two criteria considered together.

In addition to potential symptomatic efficacy, chondroitin sulphate was found to slow radiographical progression of knee OA.¹³ Because changes of joint space width were small compared with the precision error of radiography, at least 1-3 years are required to accurately assess the progression of joint damage or its reduction by treatment. To develop effective disease-modifying drugs for OA, there is an urgent need for new diagnostic techniques with improved sensitivity. A variety of biomarkers have been described to detect alterations in OA.²⁷⁻²⁸ Because OA is characterised by alterations of subchondral bone, cartilage and synovium activities, we chose to investigate the metabolism of these tissues using, respectively, CTX-I, CTX-II and S-HA, as described previously.²⁹ The association of each of these biomarkers with disease progression has been reported in knee OA.³⁰⁻³⁴ In agreement with previous studies, we found that levels of CTX-II and HA were associated with all components of radiographical knee joint damage.²⁷⁻²⁸ However, this association was modest. This is partly explained by the fact that when measured in blood or urine, levels of biochemical markers reflect OA involvement of all joints including the spine (spine disc degeneration is highly prevalent in elderly people) and not specifically the contribution of the knee.³⁵

We could not demonstrate any significant effect of chondroitin sulphate on these markers even after subgroup analyses in those with high pretreatment levels, as it has been suggested that the effect of glucosamine sulphate on CTX-II could be

Table 3 The results of the secondary end points in the chondroitin sulphate and placebo groups.

Outcome measures	chondroitin sulphate group	Placebo group	p Value
OMERACT-OARSI responders (%)	68%	56%	0.03
Change in pain at rest (VAS; mm)	-18.8 (23.8)	-16.6 (24.2)	0.366
Patient's global assessment	3.1 (3.0)	2.5 (3.1)	0.085
Investigator's global assessment	3.1 (2.7)	2.5 (3.0)	0.044
Consumption of analgesics (days)	28 (29)	28 (32)	0.962
Consumption of NSAIDs (days)	6.9 (20.2)	9.2(24.6)	0.376
Quality of life			
Mental SF-12	1.2 (10.4)	0.3 (11.3)	0.724
Physical SF-12	5.8 (9.0)	3.8 (10.2)	0.021
Carry-over effect*			
Change in pain on activity (mm)	-1.9 (20.9)	-0.4 (18.7)	0.584
Change in Lequesne's index	-0.4 (2.3)	-0.2 (2.6)	0.624

CS, chondroitin sulphate; NSAIDs, non-steroidal anti-inflammatory drugs; OMERACT-OARSI, outcome measures in rheumatoid arthritis clinical trials of the Osteoarthritis Research Society International; SF-12, short form 12; VAS, visual analogue scale.

Results are given as mean (SD).

*Carry-over effect: changes (in pain and Lequesne's Index) at the end of the follow-up (week 32) compared with the end of the treatment period (week 24).

Table 4 Mean levels of biochemical markers of bone, cartilage and synovial tissue metabolism at baseline and after 24 weeks of treatment with chondroitin sulphate or placebo

Biochemical markers	Chondroitin sulphate			Placebo			p Value on changes between groups
	Absolute baseline levels	Absolute 24-week levels	Absolute change between baseline and 24 weeks	Absolute baseline levels	Absolute 24-week levels	Absolute change between baseline and 24 weeks	
S-CTX-I (ng/ml)	0.44 (0.27)	0.44 (0.23)	0.00 (0.15)	0.39 (0.22)	0.40 (0.22)	0.01 (0.14)	0.76
U-CTX-II (ng/mmol Cr)	389 (247)	406 (302)	17.7 (241)	375 (238)	376 (214)	1.05 (170)	0.39
S-HA (ng/ml)	86 (71)	100 (86)	14.2 (73.1)	79 (61)	89 (78)	9.2 (62)	0.41

S-CTX-I, serum C-terminal crosslinking telopeptide of collagen type I; S-HA, serum hyaluronic acid; U-CTX-II, urinary C-terminal cross-linking telopeptide of collagen type II.
Results are shown as mean (SD).

Table 5 Adverse events reported in the intent-to-treat safety population (n = 309)

Adverse events	Chondroitin sulphate (n = 154)	Placebo (n = 155)
Total number of reported AEs	141	155
Number of patients with at least one AE	75 (49%)	76 (49%)
Number of patients with at least one serious AE*	10 (6.5%)	8 (5.2%)
Premature discontinuation of AEs	13 (8.4%)	8 (5.2%)

Aes, adverse events.

*One serious AE in each group was considered as possibly related to the treatment (one eczema, one urticaria)

more pronounced in patients with increased pretreatment levels.³⁶ The absence of significant effects of chondroitin sulphate on these markers may be related to a variety of possible causes including lack of power (the study was powered to demonstrate clinical efficacy). Was a 6-month treatment period long enough to modify the level of markers? It may also be possible that an effect of chondroitin sulphate could not be detected by the markers used in this study, because this drug may exert its activity on cartilage by reducing aggrecan and not collagen degradation.³⁷

Independently of treatment there was, however, a modest but significant association between clinical response (OMERACT-OARSI definition) and changes of biochemical markers over 24 weeks. Non-responders showed a significant, although limited, increase of serum CTX-I and urinary CTX-II, whereas there was a slight decrease in responders. These findings, which are consistent with those reported earlier in patients with knee OA treated with glucosamine sulphate,^{36, 38} suggest that there is a weak association between changes in bone/cartilage metabolism and changes in pain and function in knee OA.

Authors' affiliations

Bernard Mazières, Paul Sabatier University, Toulouse-3 and Department of Rheumatology, Rangueil University Hospital, Toulouse, France

Michel Hucher, Mohammed Zaïm, Institut de Recherche Pierre Fabre; Ramonville Saint-Agne, France

Patrick Garnero, INSERM research Unit 664, Lyon, France

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