A Metaanalysis of Chondroitin Sulfate in the Treatment of Osteoarthritis

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ABSTRACT. ***Objective.*** To examine the efficacy of chondroitin sulfate (CS) in the treatment of osteoarthritis (OA) on the basis of a metaanalysis of controlled clinical trials.

Methods. After personal, Medline, and Embase searches, a decision tree analysis of the available publications was performed, with respect to types of joint involvement studied, study designs, numbers of patients enrolled, and variables analyzed. The Lequesne index and pain rating on visual analog scale (VAS) were considered the main variables. Of a total of 16 publications found, 7 trials of 372 patients taking CS could be enrolled into the metaanalysis. Although all selected studies claimed to be randomized, double blind designs in parallel groups, it should be noted that CS was given along with analgesics or nonsteroidal antiiflammatory drugs, making required dosage of comedication an important factor.

Results. Following patients to 120 or more days, CS was shown to be significantly superior to placebo with respect to the Lequesne index and pain VAS. Pooled data confirmed these results and showed at least 50% improvement in the study variables in the CS group compared to placebo.

Conclusion. CS may be useful in OA, but further investigations in larger cohorts of patients for longer time periods are needed to prove its usefulness as a symptom modifying drug in OA. (J Rheumatol 2000;27:205–11)

Key Indexing Terms:
OSTEOARTHRITIS THERAPY METAANALYSIS CHONDROITIN SULFATE

Therapeutic measures in osteoarthritis (OA) consist of education, physical therapy, analgesics, nonsteroidal antirheumatic drugs (NSAID), and finally orthopedic surgery including joint replacement[1-3]. In 1994 the concept of "slow acting drugs in OA" (SADOA) was presented and approved by a WHO/ILAR conference. It was suggested to subdivide SADOA into symptomatic (SYSADOA) and disease modifying antiosteoarthritic drugs (DMOAD). SYSADOA were defined as agents without immediate analgesic effects and with a delayed onset of efficacy[4]. DMOAD are still unknown, since a disease modifying capability has not been shown for any drug currently employed for OA. More recently, antiosteoarthritic drugs were classified as either symptom modifying or structure modifying agents[5].

Most of the compounds suggested as SYSADOA or symptom modifying agents are physiological molecules contained in articular cartilage, such as chondroitin sulfate (CS) (currently available for oral application), galactosaminoglycuronoglycan sulfate (Matrix®) (which can also be applied intramuscularly)[6], or hyaluronic acid (administered directly into joint)[7]. For the orally administered drugs the pharmacological mode of action is not yet completely elucidated.

Efficacy of drugs has to be proven by randomized controlled trials (RCT) in a sufficiently large number of patients. However, to date few such studies of SYSADOA have been conducted and placebo controlled trials have included too few patients to allow unambiguous conclusions. Moreover, in OA, efficacy has to be proven over long periods of observation and also the supposed longterm effect of SYSADOA needs longer observation than treatment periods[8]. The rationale for this metaanalysis was to obtain insight into the potential efficacy of CS in light of the unavailability of large, multicenter RCT. We describe the results of a metaanalysis of the available randomized controlled studies.

MATERIALS AND METHODS

Our main objective was analysis of possible efficacy of oral CS treatment on pain and function in patients with OA. First, appropriate publications were chosen and this process was open for the searching investigator[9]. To this end, personal, Medline, and Embase searches for all available trials dealing with CS in the treatment of OA were performed using the following key words: osteoarthritis, therapy, chondroitin sulfate. A total of 16 publications were found (Table 1). These reports were then reviewed by 2 authors (BFL, HS) for methodological standards. After this review phase, by consensus of all authors, selection criteria (see below) regarding the study designs were chosen. To increase the homogeneity of the analysis, all studies dealing with OA of other localizations than hip and knee joints were primarily excluded. The remaining trials were investigated for their study design and all open, retrospective, and single blinded trials were dropped. The remaining 11 reports were listed for the type of publication, number of

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Submitted February 16, 1998 revision accepted May 28, 1999.

patients involved, study duration, characterization of the patients, and outcome measures employed. Only double blind, randomized, controlled studies in parallel groups underwent further consideration. Abstracts were not considered a potential part of the data base for this selection process, as the review experience showed lack of evaluable and comparable data in this context.

It was the consensus of the authors that any publication selected for metaanalysis had to contain data on at least half of the efficacy variables proposed by the EULAR [Lequesne Index, investigator's global assessment, visual analog scale (VAS) for pain, patient's global assessment, walking time] or SADOA guidelines [VAS of pain, functional index, Doyle index, loss of mobility, nonsteroidal antiiflammatory drug (NSAID) or analgesic consumption, number of flares over time, investigator's global assessment, quality of life scale, walking or stair climbing time][4,10]. Formal analysis of the algofunctional Lequesne index and the Huskisson pain rating by means of VAS were found to be suitable for metaanalytic evaluation of efficacy, and the analgesic and NSAID consumption available was judged at least feasible for a qualitative assessment[11].

Baseline demographics and efficacy variables had to be assessed to determine whether selected patient populations could be judged as homogeneous in the studies.

Seven of the 16 publications fulfilled all the above criteria and were selected for evaluation[12-18]. Five were published in peer reviewed journals[12-16], 6 were multicenter studies[12-15,17,18], and all were randomized, placebo controlled and double blind or double dummy trials (Table 1). The investigations evaluated showed differences concerning dosage of CS and duration of treatment. Three studies had been conducted in France, 2 in Switzerland, and one each in Italy and Hungary. They were published between 1991 and 1998 in different journals (Table 1).

A total number of 703 patients (372 treated with CS and 331 controls) were enrolled in these investigations. Patients taking active medication and the controls were well matched concerning age, sex, body weight, and stage of disease at the beginning of each of these investigations[12-18].

Furthermore we attempted to define the number of patients showing improvement by more than the minimal clinically important difference, but no trial chosen for metaanalysis provided extractable information concerning the number of patients showing a 20% or 50% improvement.

Statistical analysis of the pooled data was performed by Student's t test. Moreover, modified Glass scores of the Lequesne index and the VAS of pain at study termination using the difference of CS minus placebo results standardized by the standard deviation of the placebo group[19] were calculated. This is considered a conservative approach, as in almost all selected studies the maximum variation was observed in the placebo group at study end. In 2 studies[15,18] only percentage changes of averages against baseline were reported for the 2 efficacy variables without explicit data on standard deviations, which are needed for Glass score calculations. In these cases the Glass score calculation was based on the approximate back-calculation using independent t test formulae to the quoted p values. If analysis variables were reported for the left and right body hemisphere, averaging took place to provide uniform study effect estimates.

Actual CS dosage was considered as an important cofactor and adjusted linearly in case of different CS treatment and observation periods. This linearization, however, must be considered a first approximation. Moreover, it must be borne in mind throughout this analysis that no single publication could be found where a true placebo group was available; partly different analgesics and NSAID were used, reducing the opportunity to determine a direct influence of CS alone upon efficacy variables.

For the homogeneity evaluation, 95% confidence limits of the Glass scores were calculated. We used methods of estimating the possible influence of publication bias[19] that are based upon the non-central t distribution.

Back-translation of Glass score results into estimated population percentages benefiting from CS was based upon a Monte Carlo simulation using Mathcad 6.0 from Mathsoft Inc., USA. To provide a safe assessment of those results, the approximate 5% percentile of this proportion was calculated.

RESULTS

Based on a qualitative review of baseline demographic and disease data the pooled patient population appeared to be highly homogeneous; this could be attributable to the restriction to patients with hip and knee OA. All selected studies showed a relatively balanced number of CS and placebo patients, except one[15], where 800 mg CS was compared to 400 mg CS twice daily and placebo; this could be considered a 2:1 randomization. For reasons of transparency these 2 CS groups are shown separately as "Bourgeois a and b" in Figures 2 and 4, providing at least some insights into intra-study variation.

With respect to the crucial question of possible overall bias assessment, dropout rates in the course of the studies[12-18] are shown in Table 2. Apart from a very high value (70%) for the placebo group in the study by Conrozier[18], which was indicated as caused by lack of efficacy, all other dropout rates appeared to be relatively low.

Analysis of the main efficacy variables (pain VAS, Lequesne index). Data for the VAS pain were available and evaluable in all 7 publications[12-18] and for the algofunctional Lequesne index in 6 publications[12-15,17,18]. These data are the basis for this metaanalysis and are illustrated in Figures 1 to 4.

Pain assessed by VAS in placebo treated patients amounted to roughly 80% of baseline by Day 30, and remained between 65 and 80% of baseline value until study end (Figure 1). In contrast, VAS of pain decreased to 57% of the baseline values after 3 months in CS treated patients, reaching statistical significance at 4 months ($p < 0.05$), and further decreasing to a mean of 42% of baseline values at the end of the observation period (CS vs placebo $p < 0.005$). The changes in the individual studies ranged from 45 to 23% of baseline levels at study endpoints ($p < 0.05$ to $p < 0.001$ for the individual studies).

Pain improvement in comparison to placebo revealed an overall mean Glass score of 0.9. On the assumption of roughly normal distribution of VAS data this represents a proportion of about 65% of patients taking CS whose pain reduction was superior compared to placebo (Figure 2).

In all 6 trials containing data on the algofunctional Lequesne index, significant changes compared to baseline were seen from Day 60 onward throughout the study course in the CS patients ($p < 0.01$ to $p < 0.001$), while all the placebo groups showed no significant amelioration until study endpoint. When the results of the 6 studies were pooled, the Lequesne index at study endpoint amounted to 51% of the baseline values in the CS group, while it was > 80% of the baseline value in the controls ($p < 0.01$) (Figure 3).

The Glass score for the pooled mean Lequesne index is 0.74 and is based on about 350 patients in either study group (Figure 4). These data indicate that roughly 55% of patients will benefit from CS more than from placebo.

CS dosages and consumption of comedication. CS treatment duration showed variations from 3 to 12 months and

Table 1. Data from 16 trials of chondroitin sulfate in OA.

Author	Journal	Peer Reviewed	Study Design	Inclusion Criteria	Controls, n, Medication	CS, n, Dosage	Duration, Days	Variables Analyzed	Selected for Metaanalysis
Bahous	Swiss Med 1991; 13: 31–4	No	Retro	OA knee, hip, finger joints		25, 500 mg 3/day for 3 weeks, 500 mg 2/day for 3 months	105	Pain on movement, on pressure, on walking, NSAID consumption, VAS pain	No
Bourgeois[15]	Osteoarth Cart 1998;6 Suppl A:25–30	Yes	MC, DB	Knee OA (Kellgren I–III)	44, placebo	43, 2 × 400 mg/day for 3 months	90	Lequesne index, VAS pain, NSAID consumption, patient and physician global assessment	Yes
						40, 1200 mg/day for 3 months	90		
Bucsi[14]	Osteoarth Cart 1998;6 Suppl A:31–6	Yes	MC, DB	Knee OA (Kellgren I–III)	46, placebo	39, 2 × 400 mg/day for 6 months	180	Lequesne index, VAS pain, discomfort in daily life, patient and physician global assessment	Yes
Conrozier[18]	Lit Rheumatol 1992;14:69–75	No	MC, DB	OA hip stage I, II	27, placebo	29, 400 mg 3/day	180	NSAID consumption, Lequesne index, VAS pain, pain on pressure, motion, patient overall opinion	Yes
Crivelli	Gazette Med 1987;6:78–82	No	Open	OA of larger joints		255, 800 mg 2/day for 2 weeks, 400 mg 2/day for 13 weeks	105	Spontaneous pain, joint effusion, mobility, patients' overall opinion	No
Gross	TW 1983; 33:4238–44	No	Open	OA knee		45, 1000 or 800 mg daily for 56 days	56	Joint effusion, mobility, pain	No
Jenoure	Gazette Med 1986;7:70–9	No	Single blinded	Knee joint arthralgia	25, Salicylate/ thiamine mononitrate (500/5 mg) 3/day for 3, 2/day for 13 weeks	25, 500 mg 3/day for 3, 2/day for 13 week	102	Pain on movement, on pressure, on walking, NSAID consumption, VAS pain, arthroscopy	No
L'Hirondel[17]	Lit Rheumatol 1992;14:77–84	No	MC, DB	OA knee; joint space present	62, placebo	63, 400 mg 3/day	180	NSAID consumption, Lequesne index, VAS pain, pain on pressure, motion, walking pain, investigator's overall opinion	Yes
Leeb	Wien Med Wschr 1996;146: 609–14	Yes	Open	OA knee, hip, finger joints		61, 800 mg 2/day for 2, 400 mg 2/day for 10 weeks	90	Pain on movement, on pressure, on walking, pain at rest, pain at night, NSAID consumption	No
Maziere[12]	Rev Rheum Mal Osteoartic 1992;59:466–72	Yes	MC, DB	OA knee, hip, stage 1 (Kellgren) VAS > 4, LI > 4	56, placebo	58, 1 g bid Day 0–90, no therapy–Day 150	150	NSAID consumption, Lequesne index, VAS pain, investigator's overall opinion	Yes
Morreale[13]	J Rheumatol 1996;23: 1385–91	Yes	MC, BD	OA knee stage I, II (Kellgren)	72, diclofenac (150 mg/day) –day 30, placebo–day 180	74, 400 mg 3/day–Day 0–90, no therapy –Day 180	180	NSAID consumption, Lequesne index, VAS pain, investigator's overall opinion	Yes
Osterwalder	Gazette Med 1990;7:687–90	No	DB	Chondropathia patellae	20, placebo	18, 800 mg daily	90	VAS pain, pain on pressure, patients' and physicians' overall opinion	No
Thilo	TW Schweiz 1988; 11:893–7	No	Retro	Arthralgia		235, 500 mg 3/day for 3, 2/day for 8 weeks	77	Patients' overall assessment	No
Uebelhardt[16]	Osteoarth Cart 1998;6 Suppl A: 39–46	Yes	DB	Knee OA	23, placebo	23, 2 × 400 mg/day for one year	365	VAS pain, mobility capacity by VAS, radiological progression; cartilage markers	Yes
Verbruggen	Osteoarth Cart 1998;6 Suppl A: 37–38	Yes	DB	OA of finger joints	85, placebo	34, 3 × 400 mg/day for 3 years	1095	Radiological score	No
Wang	Lit Rheumatol 1992;14:85–9	No	DB	OA of finger joints	16, placebo	18, 400 mg 3/day in 4 cycles of 4 mo (2 mo interval)	620	VAS pain, pain on movement on pressure, NSAID consumption, radiographs	No

Retro: retrospective, MC: multicenter, DB: double blind. TW: Therapiewoche.

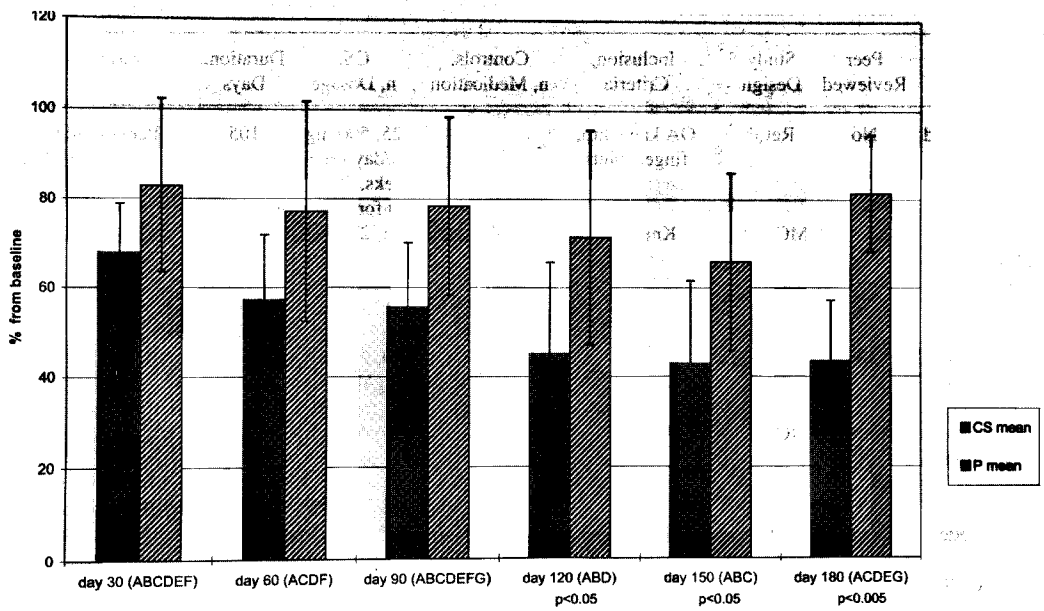

Figure 1. Pooled data on the changes of VAS pain. A: Morreale[13]; B: Maziere[12]; C: L'Hirondel[17]; D: Conrozier[18]; E: Bucsi[14]; F: Bourgeois[15]; G: Uebelhardt[16].

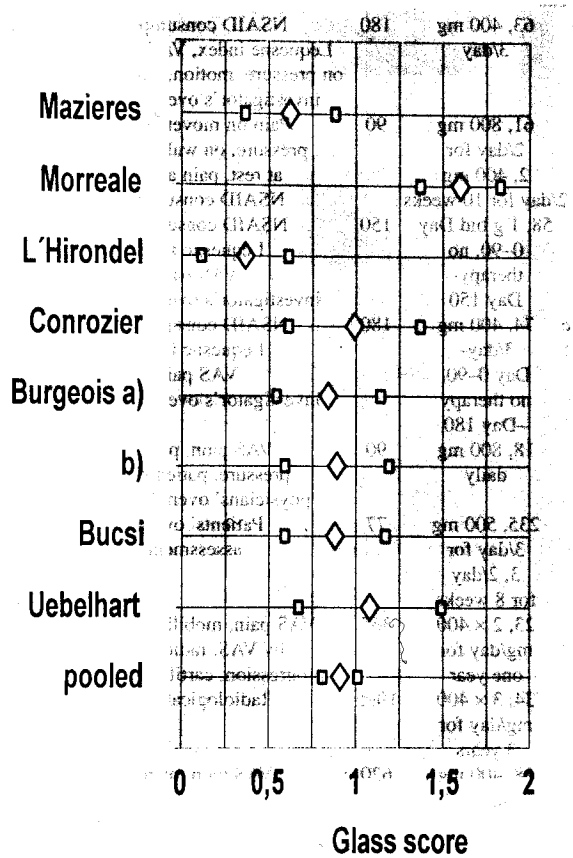

Figure 2. Glass scores for pain assessment by VAS of single trials and pooled data (mean, 95% confidence limits).

Table 2. Dropout rates of studies reviewed.

Study	CS		Placebo	
	n	Dropouts (%)	n	Dropouts (%)
Bourgeois	83	3 (3.6)	44	3 (6.8)
Bucsi	39	3 (7.7)	44	2 (4.5)
Conrozier	29	5 (17.2)	27	19 (70.4)
L'Hirondel	66	3 (4.5)	63	1 (1.6)
Maziere	58	2 (3.4)	56	1 (1.7)
Morreale	74	9 (12.2)	72	11 (15.3)
Uebelhardt	23	2 (8.7)	23	2 (8.7)
Total	372	27 (7.3)	330	39 (11.8)

prescribed CS doses extended over a range from 800 to 2000 mg daily. Correlation of dose with VAS of pain or Lequesne index showed no statistical significance, indicating that an increase of the dose did not yield better efficacy.

The underlying therapy with NSAID and/or analgesics could not be evaluated on a quantitative basis due to substantial differences in reporting. However, it is important that all 7 publications reported statistically significant reductions in consumption of NSAID and/or analgesics compared to baseline in the CS groups and much less marked reductions for placebo. This is important for assessment of improvement in the CS groups compared to placebo.

Patients' and/or physicians' global assessment. Patients' and/or physicians' global assessment within the observation

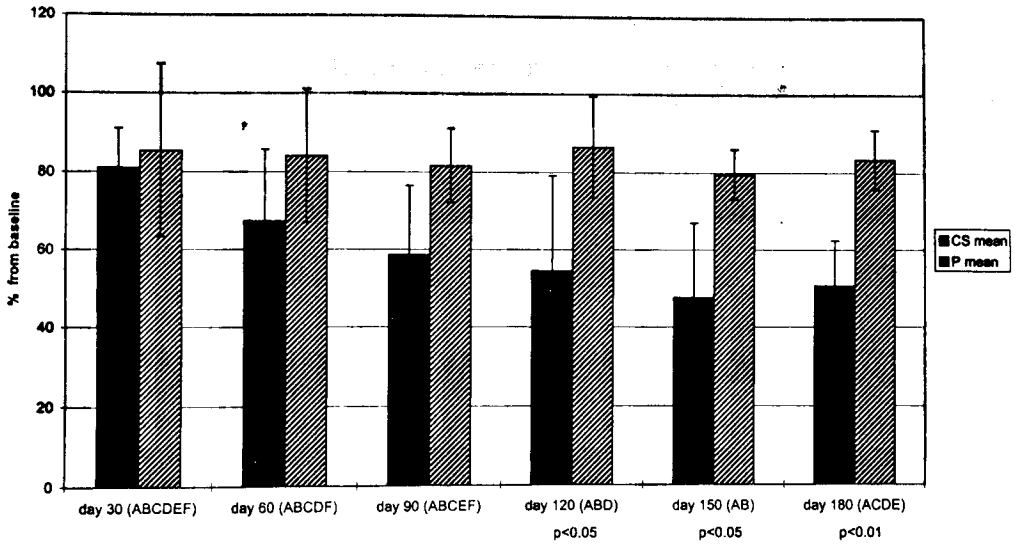

Figure 3. Pooled data on the algofunctional Lequesne index. A: Morreale[13]; B: Maziere[12]; C: L'Hirondel[17]; D: Conrozier[18]; E: Bucsi[14]; F: Bourgeois[15].

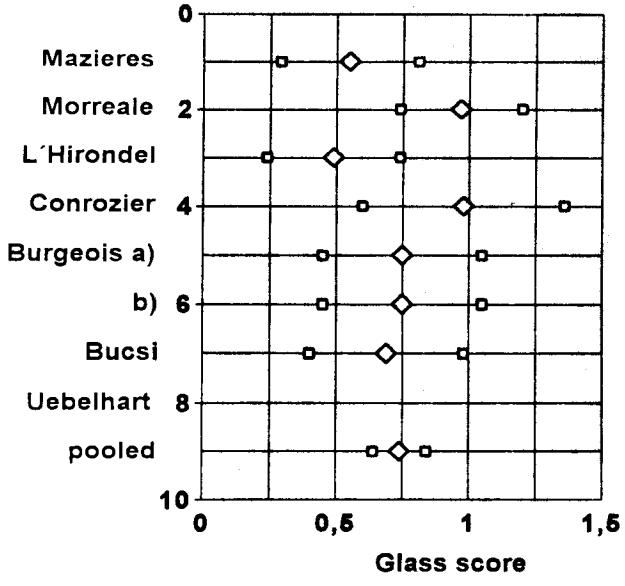

Figure 4. Glass scores for the algofunctional Lequesne index of single trials and pooled data (mean, 95% confidence limits).

period of up to 180 days was recorded in six trials[12-15,17,18]. In all investigations an advantage for the CS treatment cohort was found (Table 3). Five groups reported statistically significant differences in global assessment of therapy between CS and placebo therapy[12-15,18]. Significant superiority of CS was revealed from the results for patients' assessment in L'Hirondel's study[17].

Tolerability. Side effects were mild in all studies. They were recorded as the numbers of adverse events in patients who completed the trial. Interestingly, the frequencies of side effects were consistently higher in the placebo groups compared to the CS treated patients. Adverse events in the CS treated patients primarily affected the gastrointestinal tract, including epigastralgia (18 of 349 patients), diarrhea (n = 7), and constipation (n = 2), but skin symptoms (n = 4), eyelid edema (n = 1), lower limb edema (n = 1), alopecia (n = 1), and extrasystoles (n = 1) were also reported.

DISCUSSION

The use of CS for the treatment of OA is controversial. In particular, the mode of action is still not completely elucidated. Intestinal absorption of CS seems possible, since absorption has been shown for molecules similar to CS[20]. One study showed intestinal absorption of CS of up to 12%[21], but these results were not reproduced by other investigators. Pharmacodynamic studies revealed some antiinflammatory capacities of CS *in vitro* at higher doses than employed in the therapy of human OA[22]. In humans, changes of proteoglycan concentrations within the synovial fluid have been observed after application of CS in therapeutic doses[23]. Nevertheless, it is still uncertain if these mechanisms are responsible for the clinical effects of CS, especially since SYSADOA are supposed to show a delayed onset of efficacy.

It was the aim of this metaanalysis to evaluate the results of randomized controlled trials of CS in hip and knee OA that complied at least partly with the guidelines for investigations of drugs in OA[4,10], and in which the study drug was applied for at least 3 months. Most of the reports on CS were not published in the mainstream rheumatology literature. For some of them, flaws in their design or small sample sizes were the reasons for exclusion from this metaanalysis; however, for other publications no such restrictions were found.

Table 3. Effect of CS treatment in 6 studies.

	Morreale[13]	Conrozier[18]	Maziere[12]	L'Hirondel[17]	Bourgeois[15]	Bucsi[14]
Patient assessment	X	X	X		X	X
Physician assessment			X	X	X	X
Days	180	120	90/120	180	91	180
CS vs placebo	$p < 0.01$	$p < 0.001$	$p < 0.04/p < 0.02$	$p < 0.01$	$p < 0.01$	$p < 0.01$

The results of this metaanalysis provide evidence for some beneficial, statistically significant as well as clinically relevant efficacy of CS concerning pain and amelioration of the functional situation in patients with hip and knee OA. In these studies more than 700 patients (372 treated with CS, 331 controls) were analyzed. No study showing lack of efficacy could be found and no investigation was evaluated on an intent-to-treat basis. Although this may constitute a weakness, there were only a few dropouts, which were equally distributed between CS and placebo patients, indicating that the completer analysis may be sufficiently valid.

Analysis of the available data revealed that CS appeared superior to placebo in several respects: improvement of the algofunctional (Lequesne) index, reduction of pain, and reduction of NSAID or analgesic consumption, considered a major response criterion in OA[24]. Combining the results with the fact that all selected studies had a double blind randomized parallel group design, CS appears to affect OA positively. This was seen in each individual study, but also in combined analysis of percentage change from baseline. In particular the Lequesne index and the VAS for pain had improved by a mean of 50% in CS treated patients, but only about 20% in the controls, at the end of the studies. The estimation of possible effects of publication bias revealed a relative error of about 30%. Even if a positive publication bias led to overestimation of therapeutic efficacy, it can be concluded that the pooled data still show substantial beneficial effects of CS therapy compared to placebo. It should be noted that the publication bias estimate is based on a widely accepted statistical model[19], but statistical metaanalytic methodology can never fully compensate for systematic errors or distortions in the data not detectable after careful publication review.

Considering the pain relief results, one has to keep in mind that no complete withdrawal of analgesic medication was possible during the investigations we analyzed. In most of the trials, acetaminophen, which can also be seen as appropriate treatment of moderate OA, or low dose NSAID were allowed as additional medication in the CS as well as in the control groups[2]. Thus it may be concluded that CS in combination with analgesics or low dose NSAID is superior to analgesics or NSAID alone over longer periods in the treatment of OA. Moreover, a reduction of the required daily dose of analgesics or NSAID could be achieved. No dose finding trials for CS could be identified, and the metaanalysis did not show that differences in CS doses between individual trials resulted in sufficient clinical differences to suggest a dose-response relationship.

Patient's and/or physician's global assessment also had improved significantly in the CS versus the placebo treated patients. Other variables, such as swelling, tenderness on pressure, pain at rest and on movement, number of flares over time, and range of motion, were not available in many studies, but, when reported, also tended to favor CS[12-18].

The frequency of side effects was relatively low and not higher among patients taking CS compared to those taking placebo. However, in some studies a clear distinction between numbers of patients experiencing an adverse event and adverse event frequencies was not shown. Therefore quantitative assessment of the safety profile of CS should be reserved for future studies. The overall risk/benefit assessment of CS treatment would be incomplete without a clear safety evaluation in comparison to placebo and other standard therapies of OA. Based on a qualitative assessment of 7 studies it can be concluded that there is no safety issue to be reported concerning the use of CS. The efficacy and risks associated with longterm use of NSAID and analgesics are well documented[25-28]. Investigations dealing with application of NSAID in OA for more than 6 weeks are rare[28]. In a recent multicenter trial comparing meloxicam and diclofenac, 59.8 and 60.5% adverse events, respectively, were noted and therapy had to be withdrawn in 12.4% of the meloxicam and 18.7% of the diclofenac treated patients[29]. Thus compared to NSAID, CS was better tolerated, showing fewer side effects compared to placebo in most investigations.

Metaanalyses are commonly hampered by incongruencies with regard to the comparability of different investigations in different patient populations[11]. In this investigation, however, we saw consistent results in all publications analyzed regarding the improvement of functional capacity, reduction of pain, and tolerability in patients treated with CS compared to placebo. The methodological quality of the publications showed some differences, but at least 5 of them were published in peer reviewed journals and the results of the other 2 studies were similar. In contrast to many publications dealing with NSAID treatment of OA, the few papers concerning CS therapy are in line with the EULAR

or SADOA guidelines[4,10]. With respect to tolerability, proteoglycan preparations may have some advantages compared to longterm application of NSAID.

This metaanalysis provides evidence for significant efficacy of CS on pain and function in the treatment of OA compared to placebo in patients followed 120 or more days. With respect to pain relief, CS was apparently superior to placebo and allowed greater reduction of analgesic comedication. However, these data do not suggest that CS is generally useful in OA therapy: we identified only 7 studies that satisfied the inclusion criteria for this metaanalysis; each of these included only a relatively small number of patients; no dose finding investigations for CS could be found, and 2000 mg CS/day did not appear to be superior to a daily dose of 800 mg. Thus this metaanalysis merely suggests that CS may be useful in OA. The results should encourage larger and longer trials of CS in the treatment of OA to determine its usefulness as a symptom modifying drug in OA.

ACKNOWLEDGEMENT

We cordially thank Dr. Peter Tugwell, Chairman of the Department of Medicine, University of Ottawa, Ottawa, Canada, for reviewing our manuscript and for his important suggestions.

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