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Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration☆

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SUMMARY

Objective: To update a published meta-analysis of double-blind placebo-controlled randomized clinical trials (RCTs) to assess the efficacy of chondroitin sulfate as a structure-modifying drug for knee osteoarthritis (OA).
Design: A published meta-analysis of randomized controlled trials was updated to include data from one new trial and final data from a second trial both published recently in peer-reviewed literature. This meta-analysis was limited to three RCTs of 2-year duration. Data were pooled using a fixed effects model as there was no evidence of important heterogeneity.
Results: Pooled results demonstrated a small significant effect of chondroitin sulfate on the reduction in rate of decline in minimum joint space width of 0.13 mm [95% confidence interval (CI) 0.06, 0.19] ($P = 0.0002$) that corresponded to an effect size of 0.23 (95% CI 0.11, 0.35) ($P = 0.0001$).
Conclusion: These results demonstrate that chondroitin sulfate is effective for reducing the rate of decline in minimum joint space width in patients with knee OA.

Guidelines for the management of patients with osteoarthritis (OA) of the knee recommend a combination of non-pharmacologic and pharmacologic modalities with the goals of relieving pain and improving functional limitation and health-related quality of life[1–4]. An additional goal of therapy is limiting the progression of joint damage, often referred to as structure modification. The rate of joint space narrowing, a variable derived from serial measurements of joint space width, is currently the accepted biomarker for structural progression for purposes of design and conduct of randomized clinical trials (RCTs) for registration of products in both the United States and Europe[5]. Presently, there are no products approved either by the Food and Drug Administration in the United States or the European Medicines Agency in Europe for the indication of slowing the decline in minimum joint space width in patients with OA of the knee.

Chondroitin sulfate is a sulfated glycosaminoglycan, composed of a long unbranched polysaccharide chain with a repeating disaccharide structure of *N*-acetylgalactosamine and glucuronic acid that is incorporated into aggrecan molecules during synthesis by chondrocytes. Meta-analyses of randomized placebo-controlled trials have demonstrated the efficacy of chondroitin sulfate for relief of joint pain in patients with OA of the knee[6–10]; one of these meta-analyses also noted a small significant effect in favor of chondroitin sulfate compared with placebo for structure modification as measured by a reduction in the rate of decline in joint space width[9]. In 2008, we published the results of a systematic review and meta-analysis of all available randomized, placebo-controlled trials to determine the effects of the administration of orally administered chondrotin sulfate on the rate of change in joint space width and reported a small significant structure-modifying effect for this compound[11]. Herein we report the results of an updated meta-analysis that includes data from two recently published studies[12,13] and limits the pooling to studies of 2-year duration.

Methods

Literature search

The search strategy for the original meta-analysis has been described[11]. Briefly, the MEDLINE database was search from January 1996 through October 2007 to identify all randomized controlled

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trials (RCTs) of at least 52 weeks duration that compared orally administered chondroitin sulfate to placebo. A total of 51 articles were identified, including 31 review articles, six RCTs that reported only symptomatic outcomes in patients with knee OA or structural outcomes in patients with hand OA, five meta-analyses and four editorials as well as five articles that reported data from three RCTs of structural outcomes in patients with knee OA. These latter five articles were selected for inclusion in the original meta-analysis, along with data from one abstract presented at the 2006 annual meeting of the American College of Rheumatology (ACR). Two of these four trials were of 52 weeks duration and the other two were of 2-year duration. Since the publication of that manuscript, the final results of one of these latter trials that had been published only in abstract form as well as the results of a third trial of 2-year duration were published.

Trial selection

RCTs of 2-year duration that compared orally administered chondroitin sulfate to placebo and reported structural outcomes in the form of change in minimum joint space width were selected for inclusion in this review. No language restriction was applied.

Data extraction

Data extracted included eligibility criteria, baseline patient characteristics (age, gender, duration of OA), chondroitin sulfate dose, baseline values for Kellgren–Lawrence grade and minimal joint space width, if available, and change in minimum joint space width at the end of trial by group. The data on change in minimum joint space width were extracted by two persons.

Data analysis

The primary outcome measure was change in minimum joint space width measured in mm. The I^2 statistic was calculated to describe the percent of total variation that is attributable to heterogeneity rather than chance; values below 25% suggest low while those greater than 75% suggest high between-trial heterogeneity[14]. Because there was no evidence of moderate or greater heterogeneity, a standard fixed effects meta-analysis was used to pool data across the trials. The results were expressed in differences in change in minimum joint space width between chondroitin sulfate and placebo treated groups in mm as well as an effect size calculated from the mean difference divided by the pooled standard deviation. All analyses were performed using RevMan version 5 (Cochrane Collaboration Information Management System; www.cc-ims.net) by Dr Min Zhan.

Results

Study descriptions

The characteristics of the three studies included in the updated meta-analysis are shown in Table I. All studies were of good quality based on a Jadad score of 4 (range 0–5)[15].

Michel and colleagues randomized 300 patients aged 40–85 years who fulfilled ACR criteria for knee OA to receive either chondroitin 4- and 6-sulfate 800 mg daily (Chondrosulf; IBSA, Lugano, Switzerland) or placebo orally for 2 years[16]. The primary objective was to determine whether chondroitin sulfate delayed or halted structural changes in knee OA over 2 years. A single, partial flexion (~20°) weight-bearing posteroanterior (PA) radiograph of both knees was taken upon entry and at the end of the study or time of dropout. Minimum joint space width was measured in both knees using digitized films by a single reader blinded to time sequence using an image analysis computer according to a published method[17]. The authors analyzed data from the more severely affected compartment of the target (i.e., most symptomatic) knee using a Wilcoxon test, and reported a significant difference in favor of the chondroitin sulfate group for change in minimum joint space width in both an intention-to-treat analysis as well as sensitivity analyses limited to 225 patients with minimum joint space of 1 mm or greater at baseline and 219 patients who completed the 2-year trial.

Sawtizke and colleagues reported results from the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) ancillary study to assess structural changes in knee OA[12]. This ancillary study included 662 patients who fulfilled ACR criteria for knee OA; for the purposes of this meta-analysis we consider only those 257 patients who were randomized to receive either chondroitin sulfate 400 mg three times daily or placebo orally and were followed for up to 2 years. The primary aim of this prospective observational study of GAIT enrollees was to determine whether the supplements could have a structure-modifying effect in knee OA. A single, semiflexed, weight-bearing PA radiograph of both knees was taken upon entry and at the 12 and 24 months; the technique is that described by Buckland-Wright as the MTP view[18]. Minimum joint space width was measured in both knees using digitized films by a single reader blinded to time sequence using an image analysis computer according to a published method[18]. The authors analyzed data from the medial compartment of all affected knees with acceptable radiographs; this included 116 knees in 71 patients randomized to chondroitin sulfate and 113 knees in 70 patients randomized to placebo. The difference in favor of the chondroitin sulfate group for decline in mean joint space width, 0.059 mm, failed to reach statistical significance.

Kahan and colleagues reported results of a randomized, double-blind, placebo-controlled study in 622 patients aged 45–80 years who fulfilled ACR criteria for knee OA and were allocated to receive either chondroitin 4- and 6-sulfate 800 mg daily (Genevrier Laboratories, Sophia Antipolis, France, and IBSA, Pambio Noranco, Switzerland) or placebo orally for 2 years[13]. The two primary outcomes of this study were to determine whether chondroitin sulfate could improve symptoms and delay structure progression over 2 years in patients with knee OA. A single, partial flexion (~20–30°) weight-bearing PA radiograph of the target knee was taken upon entry and at 12, 18 and 24 months using the Lyon Schuss technique with fluoroscopy[19]. Minimum joint space width was measured in the medial compartment using digitized films by a single reader blinded to time sequence using a digital image analysis software. The authors reported a significant difference in

Table I
Characteristics of trials included in update meta-analysis

Authors, year	Dose of CS	Duration	No. enrolled in CS and PBO groups	Mean age (years)	Women (%)
Michel *et al.*, 2005	800 mg once daily	24 months	300	63	52
Sawitzke *et al.*, 2008	400 mg three times daily	24 months	257	57	68
Kahan *et al.*, 2009	800 mg once daily	24 months	622	62	68

CS = chondroitin sulfate, PBO = placebo.

Table II
Meta-analysis of change in joint space width comparing patients allocated to chondroitin sulfate vs placebo

Authors, year	CS		PBO		Mean difference (mm) (95% CI)	Effect size (95% CI)
	Mean (mm)	SD (mm)	Mean (mm)	SD (mm)		
Michel *et al.*, 2005	−0.045	0.48	0.07	0.56	0.12 (0.00, 0.23)	0.22 (0.01, 0.45)
Sawitzke *et al.*, 2008	0.107*	0.68	0.166*	0.68	0.06 (−0.17, 0.28)	0.09 (−0.24, 0.42)
Kahan *et al.*, 2009	0.07	0.03†	0.31	0.04†	0.14 (0.06, 0.21)	0.26 (0.11, 0.42)
Pooled analysis					0.13 (0.06, 0.19)	0.23 (0.11, 0.35)

CS = chondroitin sulfate, PBO = placebo, CI = confidence intervals.
* Result adjusted for baseline joint space width, sex, pain score, disease duration, weight, Kellgren–Lawrence grade, study site and weeks of treatment.
† Standard error of the mean rather than standard deviation.

favor of the chondroitin sulfate group for change in minimum joint space width in the intention-to-treat analysis. In addition, they noted a significant reduction in the proportion of subjects who had radiographic progression defined as a decline in minimum joint space width of 0.25 mm or greater.

Pooled effect on minimum joint space width

Results are shown in Table II.

There was no evidence of important heterogeneity between the trials ($I^2 = 0$); hence, a fixed effects model was used to pool the data. The meta-analysis found that patients randomized to receive orally administered chondroitin sulfate, compared to those randomized to placebo, had a significant reduction in the rate of decline in joint space width over 2 years of 0.13 mm (95% CI 0.06, 0.19) ($P = 0.0002$) that corresponded to an effect size of 0.23 (95% CI 0.11, 0.35) ($P = 0.0001$).

Discussion

The results of this meta-analysis suggest that chondrotin sulfate at a dose of 800 mg orally once daily has a small but significant effect as a structure-modifying agent in patients with symptomatic radiographic OA of the knee. These findings extend the results of our previous meta-analysis[11], and that conducted by Reichenbach and colleagues[9], and support the recommendations of the Osteoarthritis Research Society International for the use of chondroitin sulfate as a structure-modifying agent in patients with OA of the knee[3].

The present meta-analysis has several strengths. It was based on a systematic literature review performed for the original meta-analysis[11] with the inclusion of two newly published randomized placebo-controlled trials. It was limited to studies of 2-year duration and included data on over 1000 patients with symptomatic radiographic knee OA. There was no evidence of heterogeneity of results across trials allowing the use of a fixed effects model for pooling data.

This meta-analysis is, however, limited by the data from the individual trials. The individual trials included in this meta-analysis varied in source of support, size, dosing schedule for chondroitin sulfate, as well as the technique used to acquire the knee radiographs. Both the studies reported by Michel and colleagues and Kahan and colleagues were supported by industry while that reported by Sawitzke and colleagues was supported by the National Institutes of Health. The former two studies were statistically powered for assessing the primary outcome of structure modification comparing chondroitin sulfate and placebo directly. The structure modification study of GAIT, on the other hand, was designed and powered to allow comparison of structural differences across five treatment groups and only 662 of the 791 participants needed were enrolled. Furthermore, the amount of missing data exceeded expectations resulting in only 55% statistical power to detect the pre-specified 0.2 mm difference between active treatments and placebo.

While the source of chondroitin sulfate was the same across studies (all chondroitin sulfate was supplied by Bioiberica SA [Barcelona, Spain] either under license to IBSA or directly to the GAIT investigators), the dosing of chondroitin sulfate varied between studies. In the two industry supported studies, chondroitin sulfate was administered at a dose of 800 mg once daily, while in GAIT it was administered at a dose of 400 mg three times daily. It is possible that the higher drug concentrations obtained with single daily dosing might have a different pharmacodynamic effect as compared to the three times daily dosing schedule.

Despite the development of standardized protocols for obtaining reproducible radiographs for the purpose of measuring joint space width in the medial tibiofemoral compartment, there continues to be controversy about the best method for use in trials of structure-modifying agents[20]. Both the studies by Michel and colleagues and Kahan and colleagues used the Lyon Schuss position, one with fluoroscopy, while GAIT used the Buckland-Wright MTP view. All, however, used digitized films with measurement of minimum joint space width with computer-assisted techniques to reduce the measurement error and increase the precision of the measurement.

Overall, chondroitin sulfate at a dose of 800 mg orally once daily appears to have a significant but small effect of slowing the rate of joint space narrowing over a period of 2 years in patients with symptomatic radiographic knee OA. Hence, given the safety of chondroitin sulfate, it appears reasonable to administer chondroitin sulfate to patients with symptomatic radiographic knee OA for its possible structural benefit[3,21].

Conflict of interest

Dr Hochberg serves as a consultant to the following companies that have products related to the treatment of pain in patients with osteoarthritis: Allergan, Astra-Zeneca Pharmaceutical Co., Bayer Healthcare LLC, Bioiberica S.A., CombinatoRx, Covidien, Eli Lilly and Co., Ferring Pharmaceuticals, Genzyme Corporation, Merck & Co., Inc., NicOx S.A., Novartis Pharma A.G., Pfizer Inc., Pozen Inc., and Smith and Nephew. Bioiberica S.A. provides pharmaceutical grade chondroitin sulfate to IBSA under license for marketing in Europe and provided chondroitin sulfate for the Glucosamine/Arthritis Intervention Trial (GAIT).

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Maryland School of Medicine, extracted data on joint space width and performed the meta-analysis.

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