



Responder Profile to Pharmaceutical-Grade Chondroitin Sulfate: An Analysis of the CONCEPT Trial

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ABSTRACT

Introduction: The recent CONCEPT study showed that 800 mg/day of pharmaceutical-grade chondroitin sulfate (CS) was superior to placebo and similar to celecoxib in reducing pain and improving function over 6 months in patients with symptomatic knee osteoarthritis (OA). We investigate, in the present study, whether a responder profile to CS could be defined (i.e., to determine a patient's profile with the best response to treatment).

Methods: Subjects from the CS group of the CONCEPT study were included in the present analysis. Within the CS group, various subgroups were created on the basis of different categories of age, sex, body mass index, Kellgren and Lawrence grade, age since the beginning of OA, and baseline level of pain (i.e., VAS) or function (i.e., Lequesne index). The

nonparametric Kruskal–Wallis (KW) test was applied to compare the VAS pain/Lequesne index evolutions between the subgroups, and the Dwass, Steel, Critchlow, Fligner (DSCF) procedure was used to compute multiple comparisons. The impact of various covariates on the VAS pain/Lequesne index evolution was assessed by means of multiple regression.

Results: Across all analyses, the probability of response to CS treatment was significantly associated with the duration between the date of diagnosis and the initiation of treatment. In other words, the shorter the interval between the diagnosis and the beginning of the treatment, the higher the response for both pain and function, particularly for patients with a duration of less than 5 years compared to patients with a duration of 10 years or more. No other criteria were found to be consistently associated with the response to CS treatment.

Conclusion: The treatment of OA with CS has the highest chance of success if administered in the early stage of the disease. Further research with other clinical outcomes should be carried out prior to widespread application of these findings.

Trial Registration: ClinicalTrials.gov identifier, NCT03200288.

Keywords: Chondroitin sulfate; Osteoarthritis; Pain; Responders; Treatment

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Key Summary Points

In osteoarthritis, all patients are not responsive to all interventions, so it is important to define the profile of patients who will best respond to a specific intervention.

The use of prescription-grade symptomatic slow-acting drugs for osteoarthritis is proposed by some guidelines.

The treatment of osteoarthritis with chondroitin sulfate has the highest chance of success if administered in the early stage of the disease.

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis worldwide and is associated with a variety of symptoms, including pain, stiffness, and reduced physical function. The alleviation and control of symptoms is an important consideration in the clinical practice of OA treatments [1]. Many pharmacological and non-pharmacological interventions are available, and their effectiveness has been assessed in numerous randomized controlled trials and in expert reviews [2–5]. Recently, an update of the treatment algorithm for the management of OA by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) was also published and provides practical guidance for the prioritization of interventions [6]. In this algorithm, the use of symptomatic slow-acting drugs for osteoarthritis (SYSADOA) as the first-

line pharmacological therapy is proposed, despite some controversies, as highlighted by the non-recommendation of this class of drugs by some international scientific societies [3, 5]. It should indeed be acknowledged that there are many different agents in the class of SYSADOAs, including glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables, and not all agents are supported with a high level of clinical efficacy data [7]. Moreover, the quality of the same agent could be different in a pharmaceutical-grade product and an over the counter one [8]. Regarding chondroitin sulfate (CS), in a very recent meta-analysis, it was shown that CS provides a moderate benefit for pain and has a large effect on function but with some inconsistency, explained by risks of bias, brand, and study size [9].

Since it is widely acknowledged that all patients are not fully responsive to all interventions, it is important to define the profile of patients who will best respond to a specific intervention. The aim of the present study is to assess the responder profile of CS treatment using the data collected during the CONCEPT trial [10]. This was a prospective, randomized, 6-month, three-arm, double-blind, double-dummy, placebo and celecoxib (200 mg/day)-controlled trial assessing changes in pain and physical function among 604 patients with knee OA. In the study, it was shown that a CS dose of 800 mg/day is superior to placebo and similar to celecoxib in reducing pain and improving function, confirming that this particular formulation of CS should be considered a first-line treatment in knee OA management. In that study, there was no significant difference between CS, celecoxib, or placebo usage in the rate of treatment-emergent adverse events, serious adverse events, or adverse drug reactions. The CS arm of this trial was then used to investigate whether a responder profile to CS could be defined.

METHODS

The present analysis is based on the CS arm of the CONCEPT trial, a randomized controlled trial (RCT) comparing the symptomatic effect of

CS, celecoxib, and placebo in patients with knee OA [10]. Briefly, this study included patients over 50 years of age with primary knee OA diagnosed according to the clinical and radiographic criteria of the American College of Rheumatology. Patients were randomly assigned to one of the following three groups: (1) CS group: one tablet of CS 800 mg and one capsule of placebo celecoxib; (2) celecoxib group: one tablet of placebo CS and one capsule of celecoxib 200 mg; (3) placebo group: one tablet of placebo CS and one capsule of placebo celecoxib. All treatments were taken once daily, every evening with a glass of water, for 6 months. In the CONCEPT study, there were two co-primary endpoints. One primary endpoint was the change between baseline and month 6 in the patient's pain on a 100-mm visual analogue scale (VAS). The other primary endpoint was the change in the Lequesne index (LI), which integrates pain and function. Secondary endpoints included the proportion of patients reaching 20%, 40%, or 50% of minimal clinically important improvement (MCII), the patient acceptable symptom state (PASS), and the Outcome Measures in Rheumatology (OMERACT-OARSI) criteria [11–13].

The analysis was performed on the intention-to-treat (ITT) population, defined as all randomized patients who received one dose of the study medication. The results were expressed as the means and standard deviations (\pm SDs) for quantitative variables with a normal distribution and as medians and interquartile range (Q1–Q3) otherwise. Categorical variables were expressed using numbers and percentages. Values of VAS and LI measured at baseline and after 6 months were compared by Wilcoxon signed-rank test. The nonparametric Kruskal–Wallis (KW) test was applied to compare the VAS evolutions between subgroups, and the Dwass, Steel, Critchlow, Fligner (DSCF) procedure was used to compute multiple comparisons. The same statistical scheme was applied to the LI evolution. The impact of various covariates (i.e., age, body mass index, sex, Kellgren and Lawrence, time from diagnosis of knee OA, and baseline level of VAS/LI) on the VAS or LI evolution was assessed by means of multiple regression; first for each covariate

separately in a univariate model and then for all covariates combined in a multivariate model. The analysis of variance (ANOVA) or the non-parametric KW test was applied when appropriated to compare the different continuous parameters according to various responder definitions. For qualitative parameters, a chi-square test was used. The impact of the covariates (i.e., age, body mass index, sex, Kellgren and Lawrence, time from diagnosis of knee OA, and baseline level of VAS/LI) on each responder definition was assessed by means of a binary logistic regression; first for each covariate separately in a univariate model and then for all covariates combined in a multivariate model. All tests were two-sided, and the results were considered statistically significant at the 5% critical level ($p < 0.05$). Statistical calculations were carried out using the SAS statistical software package (version 9.4 for Windows).

All participating centers of the CONCEPT trial received ethics committee approval, the study was performed in accordance with the Declaration of Helsinki, and all patients provided their informed consent to participate.

RESULTS

Of the 604 patients randomized in the study, 199 received CS. In this group, the mean (SD) age was 65.5 (8.0) years, the body mass index was 30.2 (4.7) kg/m², the time from diagnosis of knee OA was 72.3 (69.2) months, and 78.34% were female.

After 6 months of CS treatment, a decrease of 35.8 (26.8) mm on the VAS was observed. The time from diagnosis of knee OA was the only significant variable associated with the VAS evolution ($p < 0.001$) using multiple regression analysis; no significant effect of age ($p = 0.48$), body mass index ($p = 0.92$), sex ($p = 0.46$), Kellgren and Lawrence ($p = 0.52$), or VAS pain level at baseline ($p = 0.12$) was observed. Patients with the shortest time since the diagnosis of OA experienced the largest improvement of pain on the VAS (Fig. 1). In fact, a decrease of 39.6 (25.9) mm was observed in patients with a time since the OA diagnosis of less than 5 years compared to a decrease of 24.7

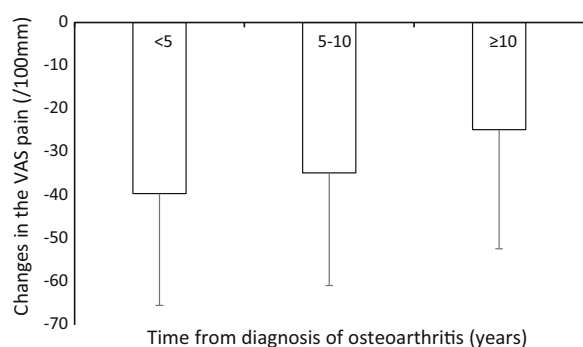


Fig. 1 Changes in the 100-mm visual analogue scale (VAS) after 6 months of chondroitin sulfate treatment according to the time from the diagnosis of knee osteoarthritis

(27.2) points in patients with a diagnosis time of more than 10 years ($p < 0.01$). Table 1 shows the clinical characteristics of the population according to time from diagnosis.

At the end of the study, a decrease of 4.09 (3.74) points on the LI was observed in the CS group. In the multiple regression analysis, only the time since the diagnosis of OA and the LI at

baseline were significantly associated with the LI change observed over the 6 months (both $p < 0.001$). Other variables such as age ($p = 0.60$), body mass index ($p = 0.97$), sex ($p = 0.44$), and Kellgren and Lawrence ($p = 0.22$) were not associated with LI change. Patients with less than 5 years since OA diagnosis experienced a median LI change of 4.50 points compared to 3.75 points for those with a diagnosis time between 5 and 10 years and 1.5 points for those with a diagnosis time over 10 years ($p < 0.05$). In patients with a baseline LI of less than 12, the median improvement was 3.50 points compared to 5.25 points for subjects with LI of 12 or more ($p < 0.01$).

Regardless of the definition that the responders considered (i.e., a 20% VAS MCII, a 40% VAS/LI MCII, a 50% VAS/LI MCII, the PASS or OMERACT-OARSI criteria), all univariate and multivariate analyses provided the same results: time since the diagnosis of OA is the only variable significantly associated with the response to the treatment. This means that the LI score at baseline was no longer associated with the

Table 1 Comparison of clinical characteristics of the study population according to time from diagnosis

Characteristics	Diagnosis < 5 years	Diagnosis 5–10 years	Diagnosis > 10 years	<i>p</i> value
Age, years	65 (59–69)	66 (59–74)	68 (63–73)	0.04*
Gender				0.39 ***
Male	32 (24.4)	4 (14.8)	7 (17.1)	
Female	99 (75.6)	23 (85.2)	34 (82.9)	
Body mass index, kg/m ²	29.6 ± 4.7	32.8 ± 4.7	30.3 ± 3.9	0.004**
Kellgren–Lawrence grade				0.02***
1	34 (25.9)	9 (33.4)	5 (12.2)	
2	67 (51.2)	13 (48.1)	20 (48.8)	
3	30 (22.9)	4 (14.8)	16 (39.0)	
4	0 (0)	1 (3.7)	0 (0)	
VAS, 0–100	71 (64–78)	71 (62–76)	71 (64–78)	0.58*
Lequesne, 0–24	11.5 ± 2.8	12.2 ± 3.5	12.4 ± 2.9	0.18**

Continuous data are presented as mean ± standard deviation when normally distributed or median (P25–P50) when skewed; categorical data are presented as absolute and relative frequencies, *N* (%)

*Kruskal–Wallis (nonparametric) test, skewed variables

**ANOVA (parametric), Gaussian distribution

***Chi² test, categorical data

probability of responding to the treatment. Of the 136 patients in the CS subgroup that had experienced an MCII of at least 20% on the VAS, 63.2% had a time since the diagnosis of less than 5 years, 24.3% between 5 and 10 years, and 12.5% over 10 years ($p < 0.01$). Similar results were observed when the OMERACT-OARSI criteria were considered: of the 132 patients who fulfilled these criteria, 65.9% had a time since the diagnosis of less than 5 years, 22.0% had a time between 5 and 10 years, and 12.1% had a time over 10 years ($p < 0.01$).

DISCUSSION

In the present study, we have shown that in patients receiving CS for 6 months, the highest improvement of pain and function was observed in patients with the shortest time since the diagnosis of osteoarthritis. These results have been observed regardless of the statistical methods used. To the best of our knowledge, this is the first time that a responder profile is proposed for the management of knee OA with CS. With one other SYSADOA, some similarities were observed. In fact, it was shown that patients with less severe structural knee OA (i.e., joint space width) experienced, over 3 years, the most dramatic disease progression (i.e., joint space narrowing) but that the use of the pharmaceutical-grade crystalline glucosamine sulfate was able to partially avoid this natural progression of the disease, while no structural effect of the treatment was observed in more severe patients [14]. Unfortunately, in that particular study, no assessment of response to the symptoms was performed. These results suggest that SYSADOAs, or at least the pharmaceutical-grade chondroitin and glucosamine sulfate, provide a better effect when given in the early stage of the disease. Few studies have been performed with other pharmacological or non-pharmacological interventions. For example, the predictors of the response to the non-steroidal anti-inflammatory drug (NSAID) rofecoxib were age of the patient, their obesity status, and the presence of concomitant diseases (e.g., depression or diabetes mellitus) [15]. During rehabilitation, the predictor of response

included sex, presence of depression or comorbidities, and the use of complementary medicine [16].

It should also be noted that our results were consistent regardless of which definition of response to treatment was used. In this particular study, and in accordance with the primary study, we have used the most common definition, i.e., the MCII, the PASS, and the OMERACT-OARSI criteria, as proposed by a group of experts [17]. It is indeed important to place additional emphasis on patients' perceptions of their clinical status in clinical trials and in clinical practice.

In our initial analyses, we observed the highest improvement in function in patients with the highest LI at baseline. However, these results were not confirmed in all of our statistical analyses, especially when different definitions of responders (i.e., MCII, PASS, OMERACT-OARSI) were taken into account. It seems quite reasonable to assume that the absolute change in the LI has the greatest probability of improving when the score is high at baseline. Consequently, the interpretation should be made with caution, even if some adjustment was performed in the analysis. However, it is interesting to note that, according to the most recent meta-analysis, CS seems to have a larger effect on function than on pain [9].

We believe that these results re-emphasize the importance of SYSADOAs as the first-line treatment in the pharmacological management of knee OA, as suggested by the recent update of the ESCEO algorithm [6]. Of course, education of the patient, promotion of physical activity, and referral to a physical therapist are the very first options of OA management and should be encouraged. However, when non-pharmacological management is no longer sufficient to restrain OA symptoms, given the limited symptomatic effect of paracetamol and the recent concerns over its safety profile in routine chronic use [6], SYSADOAs could then be used to initiate background therapy. This point of view is consolidated by the excellent safety profile of most of these SYSADOAs, especially chondroitin sulfate, as acknowledged in a very recent meta-analysis [18].

We should acknowledge some limitations of this study. First, many covariates that could potentially influence the response to treatment have not been taken into account (e.g., comorbidities, biological markers, psychological status). However, our idea was to assess responder criteria that are quite easily assessed in clinical practice. The second limitation is that the impact of compliance with the CS treatment was not assessed in our analyses. We know that compliance with treatment is a major public health problem that could have an impact on treatment effectiveness, and whether compliance could have affected our results is unknown. Third, the well-known placebo effect could play an important role in the management of OA and could then influence the interpretation of our results, but its predictors are currently not fully understood. One study protocol aimed at the identification of predictors of placebo response in OA using individual patient data meta-analysis was published in 2016, but to the best of our knowledge, the results are not yet available [19]. However, a classical meta-analysis published in 2008 showed that the placebo effect was influenced by the strength of the active treatment, the baseline disease severity, the route of delivery, and the sample size of the study [20]. Fourth, some clinical data is missing (e.g. range of motion, active knee flexion and extension, WOMAC index) which could limit the generalization of these results. Finally, our study was conducted using prescription-grade CS, and extrapolation could hardly be applied to other formulations. Indeed, both the quality and the quantity of chondroitin sulfate in food supplements are highly heterogeneous [8], and consequently, it has been highlighted that a judicious choice of chondroitin formulation is essential to maximize clinical benefit, patient adherence, and satisfaction with treatment [21].

CONCLUSION

This formulation of CS reduces pain and improves function over 6 months in a wide range of patients with symptomatic knee OA. However, the highest response to CS is observed

in patients with the shortest time between diagnosis and initiation of therapy. Our data highlight the importance of the early diagnosis of osteoarthritis to optimize its management. Indeed, when a pharmacological intervention is needed to complement the non-pharmacological treatments, CS could play an important role as the first-line treatment of knee OA, especially in the early stage of the disease.

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Compliance with Ethics Guidelines. All participating centers of the CONCEPT trial received ethics committee approval, the study was performed in accordance with the Declaration of Helsinki and all patients provided their informed consent to participate.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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