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BRIEF REPORT

Impact of chondroitin sulphate on health utility in patients with knee osteoarthritis: towards economic analysis

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Abstract

Objectives: The first objective was to assess the effect of the chondroitin 4 and 6 sulphate (CS) on health-related quality of life using utility values in patients with knee osteoarthritis (OA) during a 24-month treatment course. The second objective was, using these data, to conduct economic analyses.

Methods: Data from the STOPP study was used. This study was a randomised, double-blind, placebo (PL) -controlled trial of 2-year duration. In the STOPP study, authors assessed quality of life using the Western Ontario and McMaster Osteoarthritis Index (WOMAC). WOMAC scores were translated into Health Utility Index (HUI) scores using a specific formula. Incremental cost effectiveness ratio (ICER) was calculated taking into account the cost of CS and its effect on HUI scores, compared to PL.

Results: At baseline, the mean (SD) HUI scores were 0.59 (0.17), and 0.59 (0.18) for the PL and CS groups, respectively (p=0.31 between the two groups). The mean (SD) HUI scores changes from baseline to 6 months were 0.02 (0.02), and 0.05 (0.01) for the PL and CS groups, respectively (p=0.03). After 24 months of follow-up, HUI score increases by 0.04 (0.02) in the PL group and by 0.05 (0.02) in the CS group (p=0.37). Using the price bracket of CS in Europe, ICER assessment always resulted in a cost below €30,000 per QALY gained, after 6, 12 and 24 months of treatment.

Conclusion: CS treatment increases health utilities in patients with knee OA compared to PL over the first 6 months of treatment. Economic evaluation based on these data suggests that CS treatment could be considered as cost-effective in patients with knee OA up to a period of 24 months. A limitation in this study is the absence of direct utility assessment as well as the absence of effective treatment as comparator.

Key words: *chondroitin sulphate, economic analysis, osteoarthritis, quality of life*

Introduction

Many pharmacological treatments, including acetaminophen, non-steroidal anti-inflammatory drugs, or slow-acting drugs are currently available for patients with knee or hip osteoarthritis (OA), with symptom reduction as primary objective. These treatments, and sometimes their adverse events, have a cost. In most countries, it is presumed that good care is influenced by the funds available[1]. Therefore, in the context of health economics, it is essential to develop effective treatments and efficient strategies.

In a world with limited resources and healthcare budgets, it is important to efficiently allocate scarce resources. Economic evaluation, in OA, could be of particular interest for this purpose[2]. Unfortunately, although health economic analyses have widely been used in other diseases, relatively few data are available in OA. This could partly be because the most interesting information (e.g., utility, quality-adjusted life-year) have not frequently been collected in OA trials[3]. On the other hand, the cost-effectiveness evaluations in OA (e.g., difference between anti-inflammatory drugs or between various surgeries) using Markov models

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mainly take into account adverse events, assuming an equal symptomatic effect between treatments[4–12].

Chondroitin sulphate (CS) is a major component of the extracellular matrix from many connective tissues, including but not limited to cartilage, bone, skin, ligaments and tendons. In the articular cartilage, the high content of CS in the aggrecan plays a major role in creating considerable osmotic swelling pressure that expands the matrix and places the collagen network under tension. Several clinical trials have investigated the clinical effects of the administration of CS to patients with OA[13]. The results of these studies have been reviewed by scientific experts who concluded that CS could be an effective symptomatic treatment in OA[14–16].

Recently, a large randomised, double-blind, placebo (PL) controlled trial of 2-year duration, assessing patients with knee OA was published[17]. In this trial, long-term combined structure-modifying (i.e., X-ray) and symptom-modifying (i.e., Western Ontario and McMaster Osteoarthritis Index: WOMAC) effects of CS suggest that it could be a disease-modifying agent in patients with knee OA. Using this trial, the first objective of the present study was to assess the effect of CS on health-related quality of life using utility value during the 24-month treatment course. The second objective was, based on these data, to conduct an economic analysis.

Methods

Data from the STOPP study was used. STOPP was an international, randomised, double-blind, placebo-controlled trial in which 622 patients with knee OA were randomly assigned to receive either 800 mg CS (n=309 patients) or placebo (PL) (n=313 patients) once daily for 2 years[17]. Patients were allowed to take acetaminophen in 500-mg tablets (maximum dosage 4 g/day) for rescue analgesia and non-steroidal anti-inflammatory drugs were allowed in cases of acute pain.

Symptoms of OA were assessed by the patient's estimate of pain during the previous 48 hours, using the WOMAC. The visual analogue scale (VAS) version of the WOMAC index was used, with the patient answering each question using a 100-mm VAS. WOMAC scores were translated into Health Utility Index (HUI) scores using the previously validated formula of Grootendorst *et al* [18]. Grootendorst has developed and estimated a prediction model using linear regression to map the WOMAC along with basic demographic and OA disease severity data into HUI utility scores. The HUI is a commonly used generic preference-based instrument to measure utility. The formula used is:

Predicted HUI utility score = 0.5274776 + 0.0079767 × Pain +.0065111 × Stiffness -0.0059571 × Function + 0.0019928 × Pain × Stiffness + 0.0010734 × Pain × Function + 0.0001018 × Stiffness × Function – 0.0030813 × Pain^2 – 0.0016583 × Stiffness^2 – 0.000243 × Function^2 + 0.0113565 × Age in years – 0.0000961 × Age in years^2 – 0.0172294 × Female – 0.0057865 × Years since onset of OA in the study knee + 0.0001609 × Years since onset of OA in the study knee^2

Subsequently, the utility estimates were used to calculate the quality-adjusted life-years (QALY) using the area-under-the-curve method, that is, the weighted average of time spent in the study and utility value.

Taking into account the cost of the CS and its effect on HUI scores, compared to PL, it has been possible to assess the incremental cost effectiveness ratio (ICER), i.e. a measure of the additional cost per unit of health gain. The underlying calculation for the ICER comparing CS versus PL in patients with knee OA was:

$$\text{ICER} = \frac{\textit{Average Cost CS} - \textit{Average Cost PL}}{\textit{Average Effect CS} - \textit{Average Effect PL}}$$

where costs were measured in euros and effects were measured in QALY.

Finally, the ICERs were calculated using the minimum (€0.99/day) and maximum (€1.59/day) public costs of the branded CS treatment in Europe. Other healthcare costs and non-healthcare cost were assumed to be comparable between treatment groups.

Results

The mean baseline characteristics of the study population are summarised in Table 1. No significant difference was observed for any baseline characteristics between the CS and PL groups. Regarding utility value at baseline, the mean (SD) HUI scores were 0.59 (0.17), and 0.59 (0.18) for the PL and CS groups, respectively (p=0.31 between the two groups).

Table 1. Baseline characteristics of the study population.

	Chondroitin sulphate group	Placebo group	p-value
Women, %	69.81	66.78	0.42
Mean (SD) age, years	62.90 (9.14)	61.80 (8.51)	0.12
Mean (SD) years since OA, years	6.84 (6.16)	6.84 (6.39)	0.98
Mean (SD) Health Utility Index (HUI)	0.59 (0.18)	0.59 (0.17)	0.31

After 6 months of follow-up, the mean (SD) HUI scores changes from baseline were 0.02 (0.02), and 0.05 (0.01) for the PL and CS groups, respectively (p=0.03). After 24 months of follow-up, HUI score increases by 0.04 (0.02) in the PL group and by 0.05 (0.02) in the CS group (p=0.37).

In the CS group, the number of QALY gained after 6 months of follow-up were 0.018, 0.044 and 0.097 after 6, 12 and 24 months, respectively (Figure 1). In the placebo group, the respective QALY gains were 0.007, 0.026 and 0.072 (Figure 1).

The ICER is shown in Table 2. Using either the minimal or the maximal price of CS in Europe, ICER assessment was always below an absolute threshold of €30,000/QALY, after 6, 12 and 24 months of treatment, compared to PL.

Discussion

In this study, a statistically significant difference in terms of mean utility changes from baseline to 6 months between the CS and the PL groups was observed. No significant change after 24 months was observed. The results are comparable to the original trial results that showed a significantly faster improvement in pain in the CS group as compared to the placebo group during the first 9 months[17]. In contrast, no significant difference in pain between the two groups was observed during the second year. The main explanation, as acknowledged by the authors, for these variations is that since a significant proportion of patients had no or mild symptoms at 1 year (because of the treatment or the placebo effects), a further symptomatic effect of CS was unlikely to be observed[17].

The estimated ICER, using either the minimal or the maximal cost of branded CS in Europe, was around or less than €20,000/QALY. These results could be observed as early as the first 6 months of treatment and up to 2 years of follow-up. Using an incremental cost-effectiveness plane, the estimated ICER falls in the northeast quadrant, hence suggesting that trade-offs between costs and effects

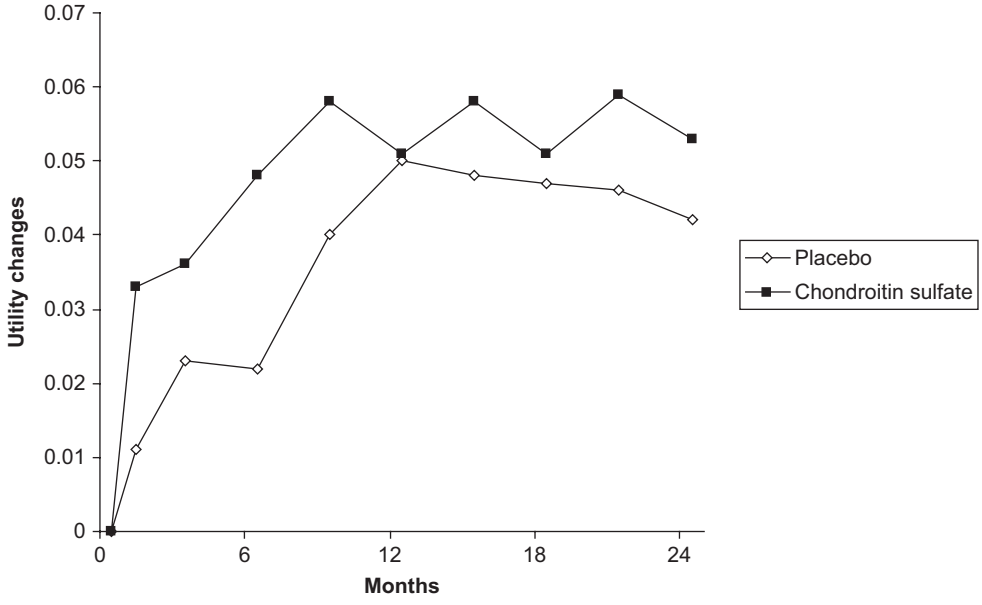

Figure 1. Utility changes during the 2 years of follow-up.

Table 2. Incremental cost-effectiveness ratio assessment.

	6 months	12 months	24 months
QALY changes in the chondroitin sulphate group, QALYs	0.018	0.044	0.097
QALY changes in the placebo group, QALYs	0.007	0.026	0.072
Minimum costs of chondroitin sulphate treatment, euros	90.41	180.82	361.64
Minimum ICER, euros/QALY	8,203.90	9,524.39	12,984.72
Maximum Costs of CS treatment, euros	145.29	290.58	581.15
Maximum ICER, euros/QALY	13,183.53	15,305.55	20,866.26

*QALY: quality-adjusted life-year; ICER, incremental cost-effectiveness ratio.

need to be considered. Such trade-offs depend upon the value at which the ICER is considered good value for money. Is €20,000/QALY a good value for money? There is no absolute answer. The decision-making process is multifactorial and depends on many elements other than efficiency, such as budget impact or preferences. Some countries have defined explicit ICER thresholds. For example, the UK currently uses an explicit threshold value of £20,000 (approximately €23,500) or £30,000 (approximately €35,000) per QALY gained[19].

The structure-modifying effect of CS has not been taken into account in this study. Indeed, in the original study, the analysis demonstrated a significant reduction (p<0.0001) in minimum joint space narrowing in the CS group compared to the PL group[17]. Given the absence of a robust association between X-ray and symptom changes[20–23], these results could hardly be used, as they state now, in economic evaluation. However, it should be acknowledged that some data showed that a higher decrease in joint space width or a greater loss of cartilage over time is associated with an increase need for joint surgery[24,25]. Further studies are needed before including structural change in pharmaco-economic models.

One of the strengths of this study is the design (i.e., RCT) in which patients were rigorously followed, providing reliable and accurate data (e.g., WOMAC). However, such design is also a weakness since compliance to treatment is higher in RCTs than in a real life setting. The international aspect of this study (i.e., that includes patients from France, Belgium, Switzerland, Austria, and the US) makes the results applicable for different countries. However, the international design has also limitation (i.e., loss of power when it comes to single country analysis, lack of homogeneity due to the combination of data from several countries). Sensitivity analysis, incorporating price bracket for CS on the European market has been performed. It should be acknowledged that utility scores were not directly measured but calculated. Moreover, HUI is only an indirect calculation of utilities. As a consequence, there might be a loss of precision. The methodology used to estimate utility from the WOMAC score has been proposed by Grootendorst in 2007[18]. The external validity of this prediction model has been reported in a recent publication[26]. Moreover, these two reports clearly state that this prediction model can be used to calculate QALYs for cost-effectiveness analysis[18,26]. A recent paper from Barton *et al* [27] suggests that the actual QALY could differ from those predicted on the basis of mapping (e.g., with the Grootendorst estimation). They compare the QALY gains, and incremental cost per QALY estimates, predicted on the basis of mapping to those based on actual EQ-5D scores of four different interventions in 389 individuals. They show that the most effective intervention was estimated to be associated with an incremental cost per QALY of £6,068, according to our preferred model, compared to £13,154 when actual data was used. Two remarks have to be made. The first is that the model recommended by Grootendorst (that was used in the current economic analysis) has not been used in the Baron paper because of the absence of useful data (e.g., time since the onset of osteoarthritis). The second point is that Grootendorst uses the WOMAC to assess utility score based on the Health Utilities Index Mark 3 (HUI3). In the Baron paper, the Grootendorst model has been used to compare estimated utility (based on HUI3) with actual utility based on EQ-5D. Another limitation is that the costs used for CS were the minimum daily costs to the public of the prescription drug in Switzerland and the maximum price in Austria. It would certainly be of interest to reproduce these analyses using the utility data and the costs of drugs country by country. Unfortunately, even if this study was international, the power of the trial would be reduced if we stratify the analysis country by country. It should also be acknowledged that these economic analyses should be considered as preliminary. As a matter of fact, a microsimulation model, taking into account adverse events or cost related to treatment strategies, should be developed and could provide new useful information. In the present analysis, no accurate compliance data was available and, added to the absence of a third group receiving traditional treatment, it has been impossible to perform bootstrapping analysis that would have been useful to better interpret the results. It should also be pointed out that these economic analyses are based on one single trial and that other studies and meta-analysis have been published on the clinical efficacy of CS. At least, the original study used a CS preparation that has been approved as a prescription drug. Therefore, the results of the current study cannot be generalised to other CS products such as those available in some countries as dietary supplements.

Conclusion

In conclusion, CS seems to be cost-effective compared to placebo but other pharmaco-economic evaluations should be performed to confirm these preliminary results.

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