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ORIGINAL RESEARCH

Cost-Effectiveness Analysis of Pharmaceutical-Grade Chondroitin Sulfate for Knee Osteoarthritis Based on Individual Patient Data from a Randomized Clinical Trial

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ABSTRACT

***Introduction*:** In a previously published randomised, placebo-controlled trial, 800 mg/day of pharmaceutical-grade chondroitin sulfate (CS) was shown to be superior to placebo in reducing pain and improving function over 6 months in patients with symptomatic knee osteoarthritis (OA). The aim of the current post hoc analyses was to evaluate the cost-effectiveness of CS compared with placebo in a European perspective using individual patient data from this clinical trial.

***Methods*:** Patients with knee OA randomised to CS or placebo were followed up at 1, 3 and 6 months. The algo-functional Lequesne index was used to derive the EuroQol Five-Dimension Five-Level (EQ-5D-5L) score based on a validated formula. The EQ-5D-5L scores at each time point were used to calculate the changes in quality-adjusted life years (QALYs) with the area under the curve method. Costs were assessed using the average price of CS in the countries where the original study took place and where CS is currently marketed. The costs of CS in three countries were then used (i.e. the Czech Republic, Italy and Switzerland). The incremental cost-effectiveness ratio (ICER) threshold for CS to be considered cost-effective was set at 91,870 EUR per QALY (equivalent to the usually recommended threshold of US $100,000). The study used an intention-to-treat population, i.e. patients who received one dose of the study drug, and imputed missing values using the basal observation carried forward method.

***Results*:** No significant differences in baseline characteristics were observed between the CS group ($N=199$) and the placebo group ($N=205$). The mean cost of CS for 6 months of treatment was 194.74 EUR. After 6 months of treatment, CS showed a mean ICER of 33,462 (95% CI 5130–61,794) EUR per QALY gained, indicating cost-effectiveness compared with placebo. The acceptability curve for cost-effectiveness shows that the CS treatment is likely to be cost-effective compared with placebo, with a 93% probability when the ceiling ratio is set at 91,870 EUR per QALY gained.

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Conclusions: These results highlight the role of CS as a cost-effective therapeutic option in the management of OA. However, further studies taking into account the use of other healthcare resources are warranted for a more complete understanding.

Keywords: Health economics; Chondroitin sulfate; Osteoarthritis; Quality-adjusted life years

Key Summary Points

Why carry out this study?

Osteoarthritis (OA) is a leading cause of disability with a significant impact on quality of life and a substantial economic burden on healthcare systems. Previous studies, including the CONCEPT trial, have shown that pharmaceutical-grade chondroitin sulfate can reduce pain and improve function in patients with knee OA.

In the context of rising healthcare costs, cost-effectiveness analyses help to optimise the allocation of limited resources. This study aims to provide critical data to inform healthcare pricing and reimbursement decisions.

What was learned from the study?

The study showed that pharmaceutical-grade chondroitin sulfate (CS) is cost-effective compared with placebo, with a mean incremental cost-effectiveness ratio of €33,462 per quality-adjusted life year (QALY) gained.

The results are consistent with previous studies, such as the STOPP trial, which also identified CS as a cost-effective intervention.

The study highlights the need for further research with longer follow-up periods and different pricing scenarios as well as with more pragmatic studies to capture real-world patient experience and refine economic evaluations.

INTRODUCTION

Osteoarthritis (OA) is a leading cause of disability in adults worldwide, with a significant impact on quality of life and a substantial economic burden on healthcare systems [1]. In the management of OA, a comprehensive approach that encompasses both non-pharmacological and pharmacological strategies is imperative [2]. Given that OA is a chronic disease, it is important to adopt treatment modalities that are not only efficacious but also pose minimal risk of adverse effects. In this context, Symptomatic Slow-Acting Drugs for OA (SYSADOAs) represent a valuable option [3]. Among SYSADOAs, chondroitin sulfate (CS) has been studied for its potential to improve joint function and reduce pain, with varying results in clinical trials [4]. Some years ago, the CONCEPT study, a prospective, randomised, 6-month trial comparing the efficacy and safety of 800 mg/day pharmaceutical-grade CS, celecoxib, and placebo was published [5]. Conducted across five European countries with 604 patients, the study measured pain reduction using the visual analogue scale and functional improvement using the Lequesne index. Results showed that both CS and celecoxib significantly reduced pain and improved function compared with placebo, with no significant differences between the two active treatments. The study concluded that CS is superior to placebo in reducing pain and enhancing function in patients with knee OA, suggesting its suitability as a first-line treatment option.

In the face of rising healthcare costs, cost-effectiveness analyses are crucial for determining the value of treatments, particularly in chronic conditions that require long-term management. In fact, in the current context of constrained resources and finite healthcare budgets, the allocation of resources to cost-effective treatments is becoming increasingly important [6]. Economic evaluations have come to play a central role in healthcare pricing and reimbursement decisions. These assessments provide critical data that influence, at least in part, the decisions made by regulatory authorities. By incorporating pharmacoeconomic evaluations into their decision-making processes, these authorities can ensure

that financial resources are used wisely to support therapies that provide the greatest health benefits relative to their costs. This strategic approach helps to maximise overall population health outcomes within budgetary constraints, making economic evaluations an essential element in the formulation of health policy and the broader strategy of healthcare management [7].

This study utilises post hoc assessment of the CONCEPT trial to evaluate the cost-effectiveness of pharmaceutical-grade CS in knee OA management.

METHODS

The CONCEPT Study

The CONCEPT study involved patients from several European countries (i.e. Belgium, Czech Republic, Italy, Poland and Switzerland) who were over 50 years old and had been diagnosed with primary knee OA according to the American College of Rheumatology's criteria [5]. Patients who had experienced significant knee pain for at least 3 months were included in the study. The primary endpoints of the study were the pain score on a visual analogue scale and the Lequesne index, both free tools. The patients were randomly divided into three treatment groups: one receiving CS and a placebo, another receiving celecoxib and a placebo, and a third group receiving double placebos. Treatments were administered daily in a double-blind, double-dummy format. The study used an intention-to-treat population, i.e. patients who received one dose of the study drug, and imputed missing values using the basal observation carried forward method. This trial was designed and monitored in accordance with the ethical principles of the International Conference on Harmonisation (ICH), the Consolidated Guideline on Good Clinical Practice (GCP), in accordance with the Declaration of Helsinki and following all other requirements of local laws. Ethics committee approval from all participating centres was obtained and all patients gave their written informed consent to participate. The central ethics committee was the Comite d'Ethique Hospitalo-Facultaire Universitaire de Liege in Belgium.

Quality-Adjusted Life Years Assessment

In the CONCEPT trial, direct measures of utility were not assessed; the study used the Lequesne index to evaluate the condition of patients with knee OA. To overcome this limitation, we used a recently validated formula from Dardenne et al. that converts Lequesne index scores into EuroQol Five-Dimension Five-Level (EQ-5D-5L) utility values [8]. This conversion formula takes into account several patient-specific factors, including the Lequesne index score, age, sex, and body mass index (BMI). More particularly, we used model number 4 under beta regression developed in the publication by Dardenne et al. It uses the following coefficients to calculate the EQ-5D-5L utility values: −0.114 for the Lequesne index, −0.0063 for age, 0.0936 for sex and 0.0165 for BMI.

In the study, estimates of EQ-5D-5L utility were used for calculating quality-adjusted life years (QALYs) through the area under the curve (AUC) method. This technique entails calculating the weighted average of the duration participants spent in the study in relation to their respective utility values. The AUC calculations were divided into three distinct time intervals: 0–1 month, 1–3 months, and 3–6 months. The total value across all the specified periods was then derived by summing the individual AUCs for each period. This is known as the cumulative AUC.

Costs of Treatment

The cost analysis of CS in the study was based on the prices of prescription-grade CS across the countries involved: Belgium, the Czech Republic, Italy, Poland, and Switzerland. However, prescription-grade CS was only available on the market in the Czech Republic, Italy, and Switzerland. For the base case scenario, the cost assessment included all available prices, irrespective of dosage, format, or packaging. This resulted in an average cost of 1.07 EUR per day per patient. In

order to conduct a sensitivity analyses, different prices were taken into account. First, the price of the cheapest packaging in each of these countries was considered. This resulted in a daily cost of 0.983 EUR per patient. Then, the least economical packaging available in each country was considered, with a cost increased to 1.53 EUR per day per patient.

Incremental Cost-Effectiveness Ratio Assessment

The cost-effectiveness analysis assessed the additional costs required to achieve an improvement in QALYs with the use of CS compared with placebo. The results were expressed as an incremental cost-effectiveness ratio (ICER), which quantifies the additional cost per QALY gained by dividing the expenditure on CS by the QALY difference between the CS and placebo groups.

To reduce variability in the ICER calculations, a bootstrap simulation with 1000 iterations was performed. This method randomly selects samples from the original dataset multiple times with replacement to generate a range of ICER estimates, thereby facilitating a comprehensive understanding of potential outcomes. In addition, the review generated cost-effectiveness acceptability curves, which show the likelihood of CS treatment being economically viable at different willingness-to-pay thresholds per QALY. This approach determines the financial feasibility of CS treatment across different economic thresholds.

The threshold value for ICERs varies significantly between countries, influenced by different methodologies and assumptions. The World Health Organization (WHO) suggests utilising a range between one and three times a country's gross domestic product (GDP) per capita as a benchmark for cost-effectiveness. However, this recommendation is not based on a methodologically rigorous background. Given that this study encompasses multiple European countries, selecting a specific GDP per capita as a baseline is challenging. A recent systematic review has indicated that a frequently mentioned threshold of US $100,000 per QALY may be more aligned with scientific discussions [9]. Consequently, in our analysis, we adopted the threshold of 91,870 EUR per QALY, equivalent to US $100,000, in order to provide a consistent benchmark across varied economic contexts. Interestingly, this threshold is within the range found using the average 2022 GDP per capita of the three countries where CS was available on the market, i.e. from 48,145 EUR for one time GDP per capita to 144,437 EUR for three times GDP per capita.

RESULTS

The demographic and baseline characteristics of patients in the CS and placebo groups were well matched. The mean age was 65.5 years (8.0) in the CS group and 64.9 years (8.0) in the placebo group, with female participants comprising 78.4% (CS) and 74.1% (placebo). BMI values were 30.2 kg/m^2 (4.7) for CS and 30.6 kg/m^2 (5.0) for placebo. The duration of knee OA diagnosis averaged 72.3 months (69.2) for CS and 69.2 months (72.5) for placebo, with Kellgren–Lawrence (KL) grades similarly distributed, with roughly 50% of the patients presenting a grade 2 OA and 25% corresponding to either a grade 1 or a grade 3 overall. Regular pain duration was 41.7 months (60.3) in the CS group and 47.8 months (68.1) in the placebo group. Baseline target knee pain scores were 70.9 mm (9.8) for CS and 70.0 mm (10.3) for placebo, while Lequesne index scores were 11.8 (2.9) for CS and 11.8 (3.1) for placebo.

The mean QALY change between baseline and month 6 was 0.0353 and 0.0296 in the CS and placebo groups, respectively (Table 1). The calculated ICER for the cost of CS under the base case scenario was 34,183 EUR per QALY gained, which is considerably lower than established thresholds for cost-effectiveness. The bootstrap method yielded a comparable ICER of 33,462 EUR per QALY (95% CI 5130–61,794). The application of the lowest and highest price limits yielded ICERs of 31,404 EUR and 48,879 EUR per QALY, respectively.

The bootstrap simulation results indicated that the CS treatment was cost-effective compared with placebo in 99% of the pairs analysed,

Table 1 Incremental cost-effectiveness ratio assessment after 6 months

Variables	Values
Incremental QALYs per patient in the CS group	0.0353
Incremental QALYs per patient in the placebo group	0.0296
Cost of placebo per patient (in EUR)	0
Cost of CS per patient (in EUR)	
Base case scenario	194.74
Lower limit	178.91
Upper limit	278.46
ICER (EUR/QALY)	
Base case scenario	
Standard method	34,183
Bootstrapping	33,462 (95% CI 5130–61,794)
Lower limit	31,404
Upper limit	48,879

CS chondroitin sulfate, *EUR* euro, *QALY* quality-adjusted life year, *ICER* incremental cost-effectiveness ratio

Table 2 Probability that pharmaceutical-grade chondroitin sulfate (CS) is cost-effective based on incremental cost-effectiveness ratio (ICER)

Limit on ICER (EUR)	Probability that CS is cost-effective (%)
0	0
10,000	0
20,000	5
30,000	37
40,000	63
50,000	78
60,000	86
70,000	90
80,000	91
90,000	93
100,000	94
110,000	95
120,000	95
130,000	96
140,000	96
150,000	96

CS chondroitin sulfate, *ICER* incremental cost-effectiveness ratio

with only 1% showing CS as less effective. The cost-effectiveness acceptability data presented in Table 2 indicates that, with a ceiling ratio of the threshold of 91,870 EUR per QALY gained, there is a 93% probability that the CS treatment offers cost-effectiveness compared with placebo (Fig. 1).

DISCUSSION

This post hoc analysis evaluated the cost-effectiveness of CS compared with placebo in managing knee OA, utilising data from a European clinical trial. Over the course of 6 months, patients were evaluated at regular intervals using the EQ-5D-5L scores derived from the Lequesne index. The costs were calculated on the basis of the average price of CS in three specific countries. The results indicate that CS, with a mean ICER of 33,462 EUR per QALY gained, was cost-effective compared with placebo taking into account the established threshold of 91,870 EUR per QALY. Finally, it should be pointed out that the 95% CI of the ICER is far below the threshold of cost-effectiveness ratio, reinforcing the economic viability of CS as a therapeutic option in OA treatment.

The current results can be compared with those of the 2009 STOPP study, both of which assessed the cost-effectiveness of CS [10]. Both studies employed a double-blind, placebo-controlled design, although there were some methodological differences between them. In the STOPP study, health-related quality of life was assessed using the Western Ontario and

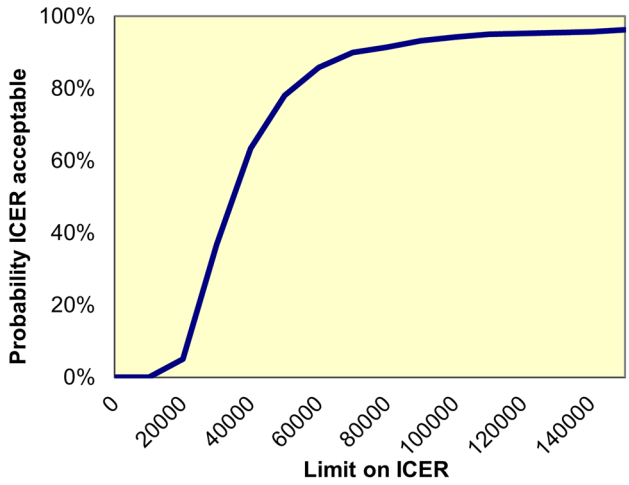

Fig. 1 Cost-effectiveness acceptability curve showing the probability that pharmaceutical-grade chondroitin sulfate is cost-effective compared with placebo over a range of values for the maximum acceptable ceiling ratio. *ICER* incremental cost-effectiveness ratio

McMaster Osteoarthritis (WOMAC) index, which was then converted into utility scores. In contrast, our study employed the Lequesne index to derive EQ-5D-5L scores, thereby providing a distinct basis for calculating QALYs. Notwithstanding the discrepancies in the employed measurement instruments, both studies have identified that CS is a cost-effective alternative to placebo. The STOPP study reported an ICER of 20,866 EUR per QALY gained at 24 months, while the present study demonstrated a mean ICER of 33,462 per QALY gained within 6 months. So, a notable difference is the duration of follow-up. The STOPP study's longer timeframe allowed for the observation of sustained effects and cost-effectiveness over 24 months, whereas our analysis was confined to a 6-month period. In addition, it should be pointed out that the cost-effectiveness analysis of the STOPP trial was published in 2009, with cost of CS from that period. Anyway, both studies indicate that CS is a cost-effective intervention for knee OA. However, this underscores the importance of further research involving extended different time-periods and different prices to fully comprehend the long-term economic consequences of CS treatment.

This study represents the first utilisation of the Lequesne index to assess QALYs within the context of an economic analysis. In the past, direct measures of health utility, such as the EQ-5D-5L, were typically employed for this purpose. The incorporation of the Lequesne index into our cost-effectiveness evaluation was made possible by the development of a novel formula that converts the Lequesne index scores into EQ-5D-5L values [8]. This novel approach paves the way for future economic analyses to utilise the Lequesne index, potentially broadening the scope of previously published clinical data that can be employed to assess the economic consequences of various treatments. It is anticipated that other studies utilising the Lequesne index will adopt this method to conduct their own economic assessments.

In the present study, we acknowledge the significance of the clinical grading of knee OA in relation to disease management and treatment outcomes. The CONCEPT study included patients exhibiting a range of severity levels of knee OA, with grades 1 to 3 of the KL scale being represented. In particular, approximately 50% of the patients exhibited grade 2 OA, while approximately 25% displayed either grade 1 or grade 3. It is notable that the minimal inclusion of patients with end-stage OA (grade 4) means that our results predominantly reflect the efficacy and cost-effectiveness of CS in patients

with mild to moderate knee OA. These findings have significant implications for clinical practice, as current guidelines advocate for a stepped treatment strategy, recommending pharmacological interventions for low grades and considering surgical options for higher grades. In light of these findings, it can be suggested that CS represents a cost-effective therapeutic option for early to moderate knee OA, in accordance with current guidelines. However, the limited number of cases in the end-stage knee OA category highlights the necessity for further research to elucidate the efficacy and economic impact of CS in more advanced stages of the disease.

One significant limitation of this study is that it focused solely on the CS and placebo arms, thereby neglecting to consider the broader spectrum of potential treatments. In addition, the economic model primarily evaluated the treatment's effect on disease symptoms without accounting for adverse events, which can substantially influence cost-effectiveness. Given the recent meta-analyses indicating that CS has a negligible adverse event profile compared with placebo [11], the cost-effectiveness comparison with other treatments with higher adverse events like oral non-steroidal anti-inflammatory drugs may be problematic. Furthermore, our analysis did not encompass all costs associated with managing OA, such as additional medications, over-the-counter products, medical visits, or broader healthcare utilisation [12]. Furthermore, although this study utilised data from a clinical trial, which ensures a high degree of data reliability and accuracy due to rigorous follow-up, it may not completely capture the everyday experiences of patients. This discrepancy indicates a necessity for the implementation of more pragmatic randomised controlled trials that employ open-label interventions and mirror real-world applications more closely. Such studies could provide a more comprehensive and relevant economic analysis, thereby enhancing our understanding of the true impact of interventions in routine clinical practice. Finally, it is important to note that the cost analysis presented in this study was based on the average price of CS from the Czech Republic, Italy, and Switzerland. Although the CONCEPT study included patients from Belgium, the Czech Republic, Italy, Poland, and Switzerland, prescription-grade CS was only available on the market in the last three countries. Accordingly, our cost-effectiveness analysis employed an average of the prices observed in these countries as a proxy for the broader European market. It is acknowledged that a weighted average approach, which takes into account the actual distribution of patients across all participating countries, could provide a more accurate representation of the treatment cost. However, this was not a viable option because of the unavailability of CS in Belgium and Poland.

CONCLUSION

This study provides valuable insights into the cost-effectiveness of CS in the treatment of knee OA. It highlights the potential of CS as a financially viable treatment option within established economic thresholds. From a public health perspective, the results support the inclusion of CS as a cost-effective intervention in treatment protocols for knee OA. This could lead to more sustainable healthcare expenditure as the prevalence of this chronic condition increases with an ageing population. Future research should aim to conduct studies in a more pragmatic, real-world setting would help to validate these findings and provide deeper insights into the practical benefits and limitations of CS treatment. Such studies are essential to inform policy makers and healthcare providers, ensure optimal resource allocation and ultimately improve outcomes for patients with OA.

Author Contributions. All authors (Olivier Bruyère and Jean-Yves Reginster) contributed to the study conception and design. Material preparation and data collection were performed by Olivier Bruyère. Statistical analysis was performed by Olivier Bruyère. The first draft of the manuscript was written by Olivier Bruyère. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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

Declarations

Conflict of Interest. Olivier Bruyère and Jean-Yves Reginster have received consulting or lecture fees from IBSA outside the submitted work. Olivier Bruyère and Jean-Yves Reginster are Editorial Board members of *Advances in Therapy*. Olivier Bruyère and Jean-Yves Reginster were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. This trial was designed and monitored in accordance with the ethical principles of the International Conference on Harmonisation (ICH), the Consolidated Guideline on Good Clinical Practice (GCP), in accordance with the Declaration of Helsinki and following all other requirements of local laws. Ethics committee approval from all participating centres was obtained and all patients gave their written informed consent to participate. The central ethics committee was the Comite d'Ethique Hospitalo-Facultaire Universitaire de Liege in Belgium.

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