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ORIGINAL RESEARCH

Analysis of the Health and Budgetary Impact of Chondroitin Sulfate Prescription in the Treatment of Knee Osteoarthritis Compared to NSAIDs and COXIBs

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Background: Chondroitin sulfate, alone or associated with glucosamine (CS), is an effective treatment of osteoarthritis, better tolerated than non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 inhibitors (COXIBs) at gastrointestinal, cardiovascular and renal levels.

Objective: To estimate the health impact (toxicity by NSAIDs/COXIBs avoided with CS with or without glucosamine) and economic impact (savings due to avoided toxicities) of treatment of knee osteoarthritis with CS compared to NSAIDs/COXIBs, as a consequence of the avoidance of mild-moderate or severe gastrointestinal adverse effects (GIAE), ischaemic heart disease (IHD), acute kidney insufficiency (AKI) and chronic kidney failure (CKF).

Methods: We compared the current situation (available reimbursed prescription with CS) with a hypothetical situation without CS (treatment only with NSAIDs/COXIBs). The frequency of GIAE, IHD, AKI and CKF with CS and NSAIDs/COXIBs was obtained from published ad hoc studies. The cost of AE management and of the drugs (180 days of treatment) was obtained from Spanish sources. A probabilistic economic model was made for a 3-year period, both at national (NHS) and regional levels. Sensitivity analyses were performed for different durations of treatment (90 and 240 days).

Results: In Spain, it is estimated that 519,130, 513,616 and 507,377 patients with knee osteoarthritis will be treated with NSAIDs/COXIBs and 112,775, 114,963 and 117,262 with CS in 2020, 2021 and 2022, respectively. Due to better CS tolerability, 55,098 mild-moderate GIAE, 3060 severe GIAE, 204 IHD, 1089 AKI and 733 CKF would be avoided in 3 years. Discounting the cost of the drugs, the three-year savings for the NHS would be 21.8 (12.7–29.5) million euros.

Conclusion: Due to its better tolerability profile, CS treatment is expected to prevent thousands of AEs over the next 3 years, some of which may be life-threatening for patients, while generating considerable savings for the NHS.

Keywords: osteoarthritis, chondroitin sulfate, glucosamine, budgetary impact, health impact

Introduction

The most recent literature suggests that chondroitin sulfate, alone or associated with glucosamine (CS), is an effective treatment for osteoarthritis, according to most of the available studies published in the period 2008–2018.[1–8] Although doubts were raised in a meta-analysis published in 2010,[9] the reliability of the results of this study was highly questioned due to possible methodological deficiencies.[10–12] On the other hand, the

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efficacy of CS has been confirmed more recently in three randomised, double-blind clinical trials in patients with knee osteoarthritis: the MOVES[4] study, in which it was found that the combination of CS with glucosamine would have similar efficacy to that of celecoxib; in the MOSAIC[5] study, in which the superiority of CS over celecoxib in reducing cartilage volume loss was demonstrated through a 2-year follow-up; and finally, in the CONCEPT[6] study, in which CS was superior to placebo and similar to celecoxib in reducing pain and improving joint function for 6 months in symptomatic patients. These results were also confirmed in a meta-analysis published in 2018.[8] CS is currently recommended for the treatment of knee osteoarthritis by, among others, the guidelines of the Spanish Society of Rheumatology,[13,14] the European League Against Rheumatism[15] and those published by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).[16]

On the other hand, as demonstrated in a recent meta-analysis,[17] CS is well tolerated. In fact, CS and glucosamine were not associated with an increased risk of adverse effects (AE) compared to placebo.[17] This good tolerability of CS contrasts with the toxicity problems described for NSAIDs/COXIBs[18] at gastrointestinal,[19] cardiovascular[20] and renal[21] levels.

In 2010 and 2017 two economic analyses[22,23] were published that analysed the efficiency of CS compared to NSAIDs. The VECTRA[22] study concluded that, compared to NSAIDs, CS is a treatment with lower costs and better gastrointestinal tolerability in the management of osteoarthritis. It was estimated that for every 10,000 patients treated with CS, 2666 gastrointestinal AEs (GIAEs) would be avoided and that, over a period of 3 years, savings of 38.7 million euros would be generated for the National Health System (NHS). The study, subsequently limited to Catalonia (Spain),[23] concluded that treatment of 67,904 patients with CS osteoarthritis instead of NSAIDs would prevent 18,103 mild-moderate and 611 severe episodes of GIAEs annually, as well as 34 ischaemic heart disease (IHD) associated with NSAIDs. The annual savings from avoiding these episodes of GIAE and IHD were estimated at 5.8 million euros and 463,000 euros, respectively.

This study's objective was to estimate the health impact (toxicity by NSAIDs/COXIBs avoided with CS) and economic impact (savings due to avoided toxicities) of the treatment of symptomatic knee osteoarthritis with CS compared to NSAIDs/COXIBs, as a consequence of the avoidance of mild-moderate or severe GIAEs, IHD and acute kidney injury (AKI) and chronic kidney failure (CKF).

Methods
Economic Model
A probabilistic economic model was performed, using a second-order Monte Carlo simulation[24–28] with two objectives: (i) to explore the effect of the uncertainty of the variables in the model (population under treatment with CS or with NSAIDs/COXIBs, probability of suffering the different AEs, AE management costs), in a hypothetical cohort of 1000 patients with symptomatic knee osteoarthritis; and (ii) to calculate the 95% CI of the main results of the analysis (AEs avoided, total savings from the AEs avoided). A probabilistic analysis was performed, considering that the frequencies of the adverse effects and the probabilities are adjusted to beta distributions and the unit costs of the adverse effects are adjusted to gamma distributions.[29]

Population
The evolution of a hypothetical cohort of patients with knee osteoarthritis was modelled. The prevalence of knee osteoarthritis in Spain, in patients over 40 years of age, was obtained from the EPISER study of the Spanish Society of Rheumatology[30] (Table 1). The population over 40 years of age in Spain (and the autonomous communities [regions]), projected for 2020–2022, was obtained from the National Institute of Statistics' database[31] (Table 1). The percentage of patients with osteoarthritis following pharmacological treatment was obtained from a study on drug use in osteoarthritis in Catalonia (Spain).[32] The percentage of patients with symptomatic osteoarthritis treated regularly or occasionally with NSAIDs/COXIBs was obtained from the same source[32] (Table 1). "Regular" use was understood to mean a medication possession ratio (MPR) ≥50% and "occasional" use with an MPR ≥ 25% and <50%.[32]

Based on these data and the number of units sold in the period July 2018 to July 2019 of Condrosan®/Condrosulf®/CS Kern and Droglican® (IQVIA market data, 2019), the number of patients with knee osteoarthritis treated with NSAIDs/COXIBs and CS with or without glucosamine in Spain and in the autonomous communities (regions) was calculated[33,34] (Table 1). Sensitivity analyses were performed based on the minimum and maximum values shown in Table 1. The details of the population calculations are presented in Table 1.

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Table 1 Population Estimates for Spain Considered in the Study

Calculation of ...	Item	Mean Value (Minimum-Maximum)	References
Prevalence of knee osteoarthritis (age ≥ 40 years)	–	13.9% (12.7–15.1%)	Seoane, 2018[30]
Population over 40 (± 1%)	2020 2021 2022	27,594,179 (27,318,237–27,870,120) 27,301,059 (27,028,048–27,574,069) 26,969,439 (26,699,744–27,239,133)	INE, 2019[31] INE, 2019[31] INE, 2019[31]
Estimated number of patients with gonarthrosis	2020 2021 2022	3,835,591 (3,469,416–4,208,388) 3,794,847 (3,432,562–4,163,684) 3,748,752 (3,390,868–4,113,109)	Calculation 1 Calculation 1 Calculation 1
% of patients with osteoarthritis receiving drug therapy	–	93.99% (93.86–94.11%)	Wilson, 2015[32]
% of patients with osteoarthritis treated with NSAIDs/COXIBs	Acc. to the MPR*	14.40%	Wilson, 2015[32]
% of patients with osteoarthritis treated with CS	Acc. to the MPR*	21.2%	Wilson, 2015[32]
No. of patients with knee osteoarthritis treated with NSAIDs/COXIBs (MPR ≥ 50%)*	2020 2021 2022	519,130 (422,029–627,345) 513,616 (417,546–620,681) 507,377 (412,474–613,142)	Calculation 2 Calculation 2 Calculation 2
No. of Droglican® units foreseen, based on annual sales up to July 2019 (± 10%)**	2020 2021 2022	392,491 (353,242–431.740) 400,341 (360,307–440,375) 408,348 (367,513–449,182)	Reig Jofre, 2019
No. of units of Condrosan®/Condrosulf®/CS Kern foreseen, based on annual sales up to July 2019 (± 10%)**	2020 2021 2022	2,993,624 (2,694,262–3,292,986) 3,053,496 (2,748,147–3,358,846) 3,114,566 (2,803,110–3,426,023)	Reig Jofre, 2019
Estimated number of patients treated with Droglican	2020 2021 2022	6934 (6241–7627) 7073 (6365–7780) 7214 (6493–7936)	Calculation 3 Calculation 3 Calculation 3
Estimated number of patients treated with Condrosan®/Condrosulf®/CS Kern	2020 2021 2022	105,775 (95,197–116,352) 107,890 (97,101–118,679) 110,048 (99,043–121,053)	Calculation 3 Calculation 3 Calculation 3

Notes: Calculation 1: 27,594,179*13.9%=3,835,591 (the rest is the same). Calculation 2: 3,835,591 *93.99%*14.4%=519,130 (the rest is the same). Calculation 3: For Condrosan®/Condrosulf®/CS Kern: (2,993,624 units*60 capsules per unit)/(2 capsules/day of Condrosan® [800 mg/day]*180 days of treatment according to their summary of product characteristics)*21.2% (MPR)= 105,775 patients (Condrosan, 2019[33]). Same for Droglican (Droglican, 2019[34]). *MPR (medication possession ratio) ≥ 50% (regular use of the drug). **An annual increase in sales of 2% is expected.
Abbreviation: CS, chondroitin sulfate with or without glucosamine.`

Variables and Scenarios Analysed

The budgetary and health impact study was performed to estimate: (i) cost of GIAEs (mild-moderate and severe) and episodes avoided with CS; (ii) the cost of IHD and episodes avoided with CS; (iii) the cost of AKI and CKF and episodes avoided with CS. To this end, the following scenarios were compared: (i) with CS: the current scenario, in which NSAIDs/COXIBs and CS, as reimbursed prescription drugs, are used for the treatment of knee osteoarthritis; (ii) without CS: a hypothetical scenario, in which only NSAIDs/COXIBs are available for the treatment of knee osteoarthritis. We compared the current situation (of patients treated with CS or NSAIDs/ COXIBs, 18% would be treated with CS and 82% with NSAIDs/COXIBs) with a hypothetical situation without CS (100% treated with NSAIDs/COXIBs). The objective of this comparison was to estimate and highlight the health and economic contribution of CS in the treatment of knee osteoarthritis.

An analysis was carried out for the national population and a sub-analysis at the regional level.

Time Horizon

The simulation covered a period of 3 years (2020 to 2022). Health and economic impacts were calculated for annual cycles.

Perspective of the Analysis

That of the NHS, so only direct health costs were considered.

Costs Analysed

The following costs were analysed: (i) the cost of managing AEs (mild-moderate or severe GIAE, IHD, AKI and CKF); (ii) the cost of acquiring the drugs (CS with or without glucosamine, NSAIDs/COXIBs). The costs are presented in euros (€) updated to 2019.

Costs and Probabilities of AEs

The unit costs of handling the AEs analysed are shown in Figure 1. The probabilities of the appearance of the different AEs are presented in Figure 2.

GIAE

The unit costs of a mild-moderate GIAE (€240) and a severe GIAE (€2857) were obtained from the VECTRA[22] study, whose original source was the public prices of the regions (Figure 1).

The annual probabilities of suffering a mild-moderate GIAE (0.64% with CS; 16.19% with NSAIDs/COXIBs) or severe (0% with CS; 0.42% with NSAIDs/COXIBs) GIAE were obtained from the GI-REASONS[19,35] study (Figure 2). In the GI-REASONS study, 10 and 18 severe and 415 and 683 mild-moderate GIAE with celecoxib and NSAIDs, administered over 6 months, were reported in a cohort of 3970 and 3951 patients with osteoarthritis, respectively.[19,35] On the other hand, according to the Spanish Agency of Medicines and Medical Devices,[36] COXIBs and NSAIDs
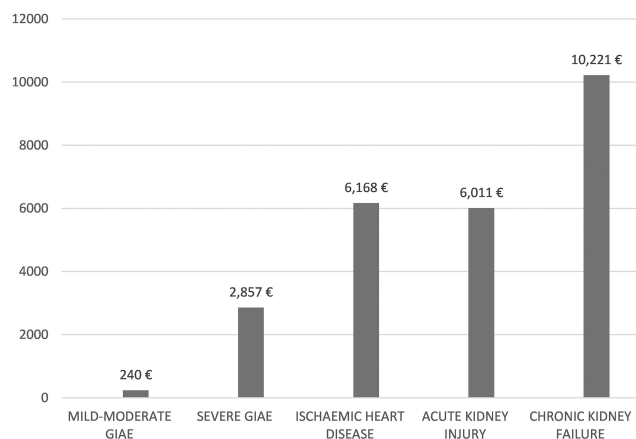
are used in 16.08% and 83.92% of patients, respectively. Consequently, the annual probabilities of suffering from a GIAE were calculated. For example, the probability of mild-moderate GIAE with NSAIDs/COXIB would be [10.45%*16.08%] + [17.29%*83.92%] =16.19%. These assumptions are more conservative than those adopted in the previously published VECTRA study.[22]

IHD

The economic impact of IHD was calculated from the public prices of DRG 121, 122, 123 and 140[23,37] according to the frequency observed in the study by the Jordi Gol Primary Care Research Institute[20,23] (Figure 1). According to this study, the probability of a patient with osteoarthritis treated with NSAIDs/COXIBs suffering from a coronary ischaemic event would be 0.120% (0.105–0.139%). In the case of treatment with CS it would be 0.070% (0.063–0.077%)[20,23] (Figure 2).

These estimates were calculated considering that NSAIDs increase the risk of IHD only in patients at high cardiovascular risk, according to the study by De Abajo et al,[38] and that these patients are 50% of the total patients with vascular risk, according to the aforementioned Catalonian study.[20] The increased risk of ischaemic stroke associated with NSAIDs, not considered in this study, has also been highlighted in another published Spanish study.[39]

AKI and CKF

The economic impact of AKI and CKF was calculated from public health prices[40] (Figure 1). The frequency of AKI (0.31%) and CKF (0.21%) associated with NSAIDs/COXIBs was obtained from the study by Nelson et al,[21] a retrospective study that included a large cohort of patients in the USA, treated with NSAIDs/COXIBs for at least 7 months of observation (Figure 2).

Drugs Costs

The average annual cost of treatment with CS was calculated as indicated in Table 2.[33,34,41] The average cost of CS and NSAIDs/COXIBs was calculated for different durations of treatment over the period of 1 year: 180 days (6 months) in the base case of the analysis and 90 or 240 days (3 or 8 months) for the sensitivity analysis. According to its summary of product characteristics, CS treatment should be carried out for at least 3 months, although in patients with significant inflammatory symptoms, after a rest period of 2 months, treatment could be started again following the same cycle.[33] Therefore, over the period of 1 year, CS treatment could range from
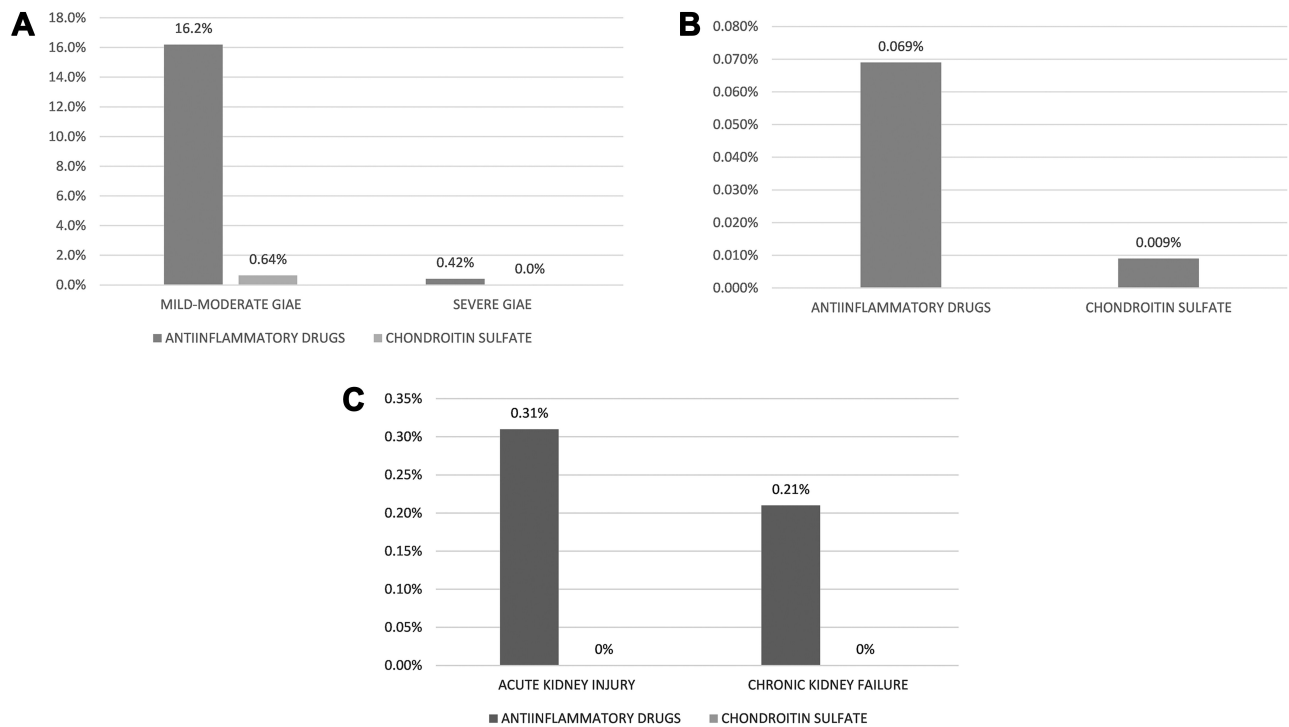

Figure 1 AE management costs.
Note: Data from these studies.[22,23,40]
Abbreviations: AE, adverse effects; GIAE, gastrointestinal AE.

Figure 2 Probability of the appearance of AEs with CS or anti-inflammatory drugs (NSAIDs/COXIBs). (**A**) Gastrointestinal AE; (**B**) ischaemic heart disease; (**C**) acute kidney injury/chronic kidney failure.
Note: Data from these studies.[19–21]
Abbreviations: AE, adverse effects; GIAE, gastrointestinal AE; CS, chondroitin sulfate with or without glucosamine; IHD, ischaemic heart disease; AKI, acute kidney injury; CKF, chronic kidney failure.

a minimum of 3 months to a maximum of 8 months. In the case of CS with glucosamine, it is advisable to administer it for a period of at least 6 months.[34] With respect to NSAIDs/COXIBs, the duration of the treatment is highly variable, depending on the different studies. In the GI-REASONS[19,35] study, a randomised clinical trial aimed

Table 2 Average Cost per Patient of Treatment with CS

Item	CS	CS + GLU	References
Pharmaceutical form	Capsules	Capsules	Condrosan, 2019[33] Droglican, 2019[34]
Drug	CS	CS/Glucosamine	
Dose/unit (mg)	400	1200/1500	
No. of units	60	90	
Retail Price	€15.50.	€17.80	BotPlus, 2019[41]
Price/unit	€0.26*	€0.20	Calculation 1
Dose/day (mg)	800	7200/9000	Condrosan, 2019[33] Droglican, 2019[34]
No. of units/day	2	6	
Cost/day	€0.52*	€1.20	Calculation 2
Duration of Treatment Base case (A. sensitivity)	180 days (90 and 240 days)		Condrosan, 2019[33] Droglican, 2019[34]
ANNUAL cost per patient Base case (A. sensitivity)	**€93.60* (€46.80 – €124.80)**	**€216.00 (€108.00 – €288.00)**	Calculation 3

Notes: *Calculation 1: €15.50/60= €0.26; Calculation 2: €0.26 x 2= €0.52; Calculation 3: €0.52 x 180= €93.60.
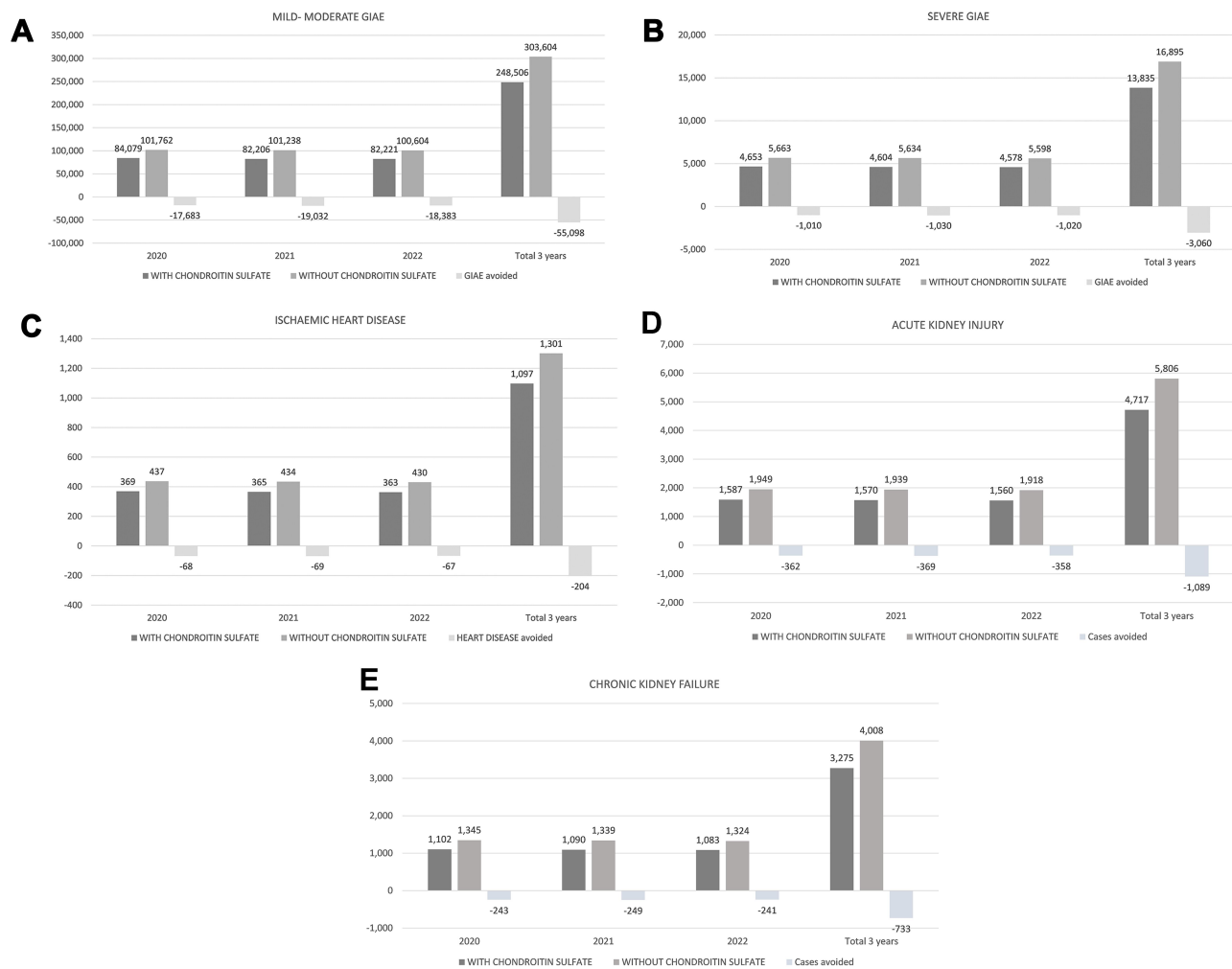**Abbreviations:** CS, chondroitin sulfate; CS+GLU, CS with glucosamine.

Figure 3 Estimated frequency of AE with and without CS. (**A**) Mild-moderate GIAE; (**B**) Severe GIAE; (**C**) Ischaemic heart disease; (**D**) Acute kidney injury; (**E**) Chronic kidney failure.
Abbreviations: AE, adverse effects; CS, chondroitin sulfate with or without glucosamine; GIAE, gastrointestinal AE.

at analysing the GIAEs associated with celecoxib and the NSAIDs/COXIBs, treatment duration was 6 months. This study was used to obtain the average frequency of GIAEs with NSAIDs/COXIBs used in the economic model. Consequently, an average treatment duration of 180 days, between a minimum of 30 and a maximum of 240 treatment days per year, was considered in the base case.

The average cost per patient treated with NSAIDs/COXIBs in the base case (180 days of treatment) was estimated at €45.68.[36,42] It was calculated from the report on the use of non-steroidal anti-inflammatory drugs in Spain during the period 2013–2016, published by the Spanish Agency of Medicines and Medical Devices[36] and from current prices by homogeneous grouping published by the Ministry of Health.[42] The daily doses of the various NSAIDs/COXIBs were obtained from the VECTRA[22] study.

Base Case and Sensitivity Analysis

The base case was analysed for a treatment duration of 180 days. Sensitivity analyses were performed for treatment durations of 90 and 240 days.

Results
National Results

In Spain, it is estimated that 519,130, 513,616 and 507,377 patients will be treated with NSAIDs/COXIBs with knee osteoarthritis and 112,775, 114,963 and 117,262 with CS in 2020, 2021 and 2022, respectively.

Due to the improved tolerability of CS, 55,098 mild-moderate GIAE, 3060 severe GIAE, 204 IHD, 1089 AKI and 733 CKF would be avoided in 3 years (Figure 3).

Discounting the cost of the drugs, the three-year savings for the NHS would be 21.8 (12.7–29.5) million euros.

Table 3 Economic Impact of Knee Osteoarthritis Treatment with/without CS

Treatment Duration (Days)	Year	Savings from Avoiding AE	Additional Cost of the CS	Net Savings from Avoiding AE with the CS	Probability of Savings with CS
180	2020	€13,540,448	€6,249,466	€-7,291,022	72.2%
	2021	€13,774,179	€6,374,456	€-7,399,724	
	2022	€13,630,133	€6,501,945	€-7,128,188	
	Total	**€40,944,800**	**€19,125,867**	**€-21,818,933**	
90	2020	€12,907,221	€3,124,733	€-9,782,488	74.0%
	2021	€13,148,524	€3,187,228	€-9,961,296	
	2022	€13,008,602	€3,250,927	€-9,757,629	
	Total	**€39,064,347**	**€9,562,934**	**€-29,501,413**	
240	2020	€12,492,110	€8,332,622	€-4,159,488	68.0%
	2021	€12,735,315	€8,499,274	€-4,236,040	
	2022	€12,957,509	€8,669,260	€-4,288,249	
	Total	**€38,184,934**	**€25,501,156**	**€-12,683,778**	

Abbreviation: CS, chondroitin sulfate with or without glucosamine.

The probability of savings with CS alone or associated with glucosamine was 72.2% (74.0–68.0%) (Table 3).

Regional Results

The regional results are presented in Table 4.

Discussion

According to this study, due to its improved tolerability profile, CS treatment is expected to prevent thousands of AEs over the next 3 years, some of which may put patients' lives at risk, while generating considerable savings for the NHS.

In assessing these results, we must consider their strengths and weaknesses. The consistency of the sources used to obtain the main variables of the analysis can be considered a strength of the study. Given that the study is an economic model, the population and adverse effect frequency data were obtained, respectively, from epidemiological studies or data[30,31] and from clinical megatrials[19] or observational studies.[20,21] The prevalence of knee osteoarthritis in Spain was obtained from the EPISER study of the Spanish Society of Rheumatology.[30] The population over 40 years of age in Spain was obtained from the National Institute of Statistics' database.[31] The percentage of patients with osteoarthritis following pharmacological treatment was obtained from a study on drug use in osteoarthritis in Catalonia.[32] Finally, the percentage of patients with osteoarthritis treated regularly or occasionally with NSAIDs/COXIBs was obtained from the same source,[32]

a Spanish study that included 238,536 participants, followed between 2006 and 2010.

Although it should be remembered that this is a theoretical model (which is, by definition, a simplified simulation of reality), a probabilistic model was carried out designed to explore the effect of the uncertainty of the variables in the model and calculating the 95% CI of the main results of the analysis (AEs avoided, total savings from AEs avoided). This type of model allows a better simulation of clinical reality.[24–29]

The results obtained in this study are consistent with those of two previously published Spanish economic analyses.[22,23]

With regard to the weaknesses, perhaps the most noteworthy is the calculation of the estimated number of patients treated with CS or NSAIDs/COXIBs. However, this number was calculated according to the available epidemiological and population data and was the subject of a sensitivity analysis as shown in Table 1.

The study did not consider patients receiving CS and NSAIDs concomitantly, which is estimated to be 12% of patients treated with CS according to the VECTRA[22] study and 2.17% in the study by Wilson et al,[32] and should therefore also be considered a limitation of the study.

Conclusions

Due to its improved tolerability profile, CS treatment is expected to prevent thousands of AEs over the next 3 years, some of which may be life-threatening for patients, while generating considerable savings for the NHS.

Table 4 Estimated Costs (€) of GIAE, IHD, AKI and CKF, Additional Costs and Costs Avoided with CSs. By Autonomous Community (Region)*

Region	Savings from Avoiding Adverse Effects (€) with CS				Additional Cost with the CS (€)				Total Savings with CS (€)			
	2020	2021	2022	Total	2020	2021	2022	Total	2020	2021	2022	Total
Andalusia	2,167,633	2,206,403	2,224,746	6,598,782	1,017,194	1,037,538	1,058,288	3,113,020	-1,150,439	-1,168,865	-1,166,458	-3,485,762
Aragon	470,624	480,791	490,623	1,442,038	267,730	273,085	278,547	819,362	-202,894	-207,706	-212,076	-622,676
Asturias (Principality of)	413,734	421,762	424,067	1,259,563	199,744	203,739	207,814	611,297	-213,990	-218,023	-216,253	-648,266
Balearic Islands	357,868	364,344	364,565	1,086,777	175,742	179,257	182,842	537,841	-182,126	-185,088	-181,723	-548,937
Canary Islands	695,922	709,298	737,628	2,142,848	358,053	365,214	372,518	1,095,786	-337,869	-344,084	-365,110	-1,047,063
Cantabria	163,950	167,295	169,644	500,889	82,274	83,919	85,598	251,791	-81,676	-83,375	-84,046	-249,097
Castile and Leon	1,025,191	1,044,842	1,085,188	3,155,221	483,006	492,666	502,519	1,478,191	-542,185	-552,176	-582,669	-1,677,030
Castile-La Mancha	702,968	717,258	749,535	2,169,761	354,022	361,103	368,325	1,083,449	-348,946	-356,155	-381,210	-1,086,311
Catalonia	789,246	810,864	811,486	2,411,596	493,250	503,115	513,178	1,509,544	-295,996	-307,749	-298,308	-902,053
Valencian Community	1,398,288	1,425,854	1,469,272	4,293,414	639,929	707,808	721,964	2,123,701	-704,359	-718,046	-747,308	-2,169,713
Extremadura	734,002	748,707	762,796	2,245,505	337,718	344,472	351,361	1,033,551	-396,284	-404,235	-411,434	-1,211,953
Galicia	704,148	717,488	718,655	2,140,291	322,517	328,967	335,547	987,031	-381,631	-388,521	-383,108	-1,153,260
Madrid (Community of)	1,121,764	1,148,706	1,186,147	3,456,616	679,380	692,968	706,827	2,079,175	-442,384	-455,738	-479,320	-1,377,442
Murcia (Region of)	849,462	866,447	888,364	2,604,273	482,219	491,864	501,701	1,475,784	-367,243	-374,583	-386,663	-1,128,489
Navarra (Autonomous Community of)	177,173	180,852	188,083	546,108	87,452	89,201	90,985	267,637	-89,721	-91,651	-97,098	-278,471
Basque Country	385,618	392,892	394,109	1,172,619	181,021	184,641	188,334	553,996	-204,597	-208,251	-205,775	-618,623
Rioja (La)	60,965	62,448	64,076	187,490	34,216	34,900	35,598	104,714	-26,749	-27,548	-28,478	-82,775

Notes: *It should be noted that the sum of the costs of AEs estimated for the regions is approximately (not exactly) that obtained at the national level (Table 3). The difference in the results is due to the following reasons: (1) each probabilistic analysis (the national analysis and that of each region) is independent of the other analyses, unique and unrepeatable, and therefore, the results of the parts do not exactly add up to the total of the independent analysis on a national level; and (2) because in the analysis on a regional level, Ceuta and Melilla are not included.
Abbreviations: CS, chondroitin sulfate with or without glucosamine; IHD, ischaemic heart disease; GIAE, gastrointestinal adverse effects; AKI, acute kidney injury; CKF, chronic kidney failure.

Copyright/Ethics

Funding

Disclosure

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