Economic impact of steroid-induced comorbidities in severe asthma: a SHARP CRC simulation

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Shareable abstract (@ERSpublications)
Reducing the use of oral corticosteroids (OCS) in severe asthma is now a key clinical objective; health economic modelling of OCS-sparing strategies indicates that early action would have a tangible, positive impact on the cost of OCS-related comorbidities https://bit.ly/3YBvfp9

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Abstract

Background Patients with severe asthma (SA) consume roughly 50% of the global asthma healthcare resources due to unscheduled visits, hospitalisations, therapy and management of oral corticosteroid (OCS)-related adverse events (AEs). Biologics offer a route away from continuous OCS treatment. Asthma management guidelines discourage OCS usage, particularly when continuous and at high doses because of increased risk of OCS-AEs. This study simulates the economic burden over 10 years of reversible OCS-AEs (hypertension, psychiatric conditions, sleep disorders, dyspepsia) in SA patients in 11 European countries.

Methods The focus of this study was exclusively on the economic burden of AEs resulting from continuous OCS use in SA patients. For each country, a budget impact model estimated total AE costs in SA patients in various OCS sparing scenarios. AE costs arising from daily OCS use (reference cost) were compared to AE costs when a percentage of patients annually stops OCS, and the rate of OCS-related AEs decreases. Epidemiological data, OCS-AE prevalence values and costs were literature-based.

Results Analysis showed potential cost reductions of 13.1% to 31.6% in terms of OCS-related comorbidities over 10 years among SA patients. The size of the saving depends on the rate of onset of comorbidity, the reversibility of OCS comorbidities and the proportion of the population stopping OCS each year.

Conclusion Stopping OCS has the potential to yield substantial, long-term AE savings in SA patients.

Introduction

Between 3.5% and 10% of patients with asthma have severe disease [1–5], defined by difficult-to-treat symptoms that remain uncontrolled despite medium-to-high doses of inhaled corticosteroids (ICS) with a second controller (usually long-acting β-agonists), often leading to recurrent bursts and/or maintenance oral corticosteroids (OCS), mostly because symptoms tend to worsen whenever high-dose maintenance treatment is decreased [6].

Poor symptom control is burdensome to severe asthma (SA) patients and increases the risk of exacerbations. Although SA patients represent a small percentage of all patients with asthma, they consume ∼50% of the global asthma budget due to unscheduled healthcare utilisation in primary care, hospitalisations because of severe exacerbations, costs of pharmacotherapy and management of OCS side-effects [7–9]. A recent analysis in the UK showed that the healthcare costs per SA patient are higher than those of patients with type 2 diabetes, stroke or COPD [10]. In a Canadian study, uncontrolled SA was estimated to account for >60% of asthma costs [11].

Medication side-effects are particularly common and problematic when using OCS [12–14], drugs that were a mainstay of treatment for SA before the era of asthma biologics. Adverse events (AEs) of long-term OCS use (OCS AE) are progressively understood as the key argument for developing alternative strategies as OCS is associated with the development of obesity, diabetes, osteoporosis, cataracts, hypertension, adrenal suppression and other life-changing conditions [15]. Psychological side-effects, such as depression and anxiety, are particularly distressing for SA patients [16]. Even short-term use of OCS is associated with sleep disorders, increased risk of infection, fracture and thromboembolism [17]. Therefore, strategies to minimise the use of OCS are paramount. In this regard, three of the currently approved biologics (mepolizumab, benralizumab and dupilumab) have demonstrated strong efficacy and a significant OCS sparing effect [18–20]. To inform both payors and policymakers, it is worthwhile to quantify the extent to which savings associated with OCS sparing can offset the costs of biologics. Unfortunately, to date, the economic burden of OCS-induced AEs remains largely unknown. Moreover, long-term, real-world studies are difficult to justify, and historic comparisons are only partly relevant; thus, this question remains largely unanswered.

The aim of the current study was to quantify the economic consequences of comorbidity-induced AEs due to maintenance OCS use in SA patients over a long time horizon (10 years) using a budget impact model (BIM). The BIM allowed us to simulate various OCS sparing scenarios and to estimate the economic burden of OCS-ascribable AEs.

Materials and methods

BIM design

The BIM was based on a published model initially developed for use in Italy [1], which was updated and extended to simulate costs in 11 European countries, namely, Belgium, Denmark, France, Hungary, Italy, the Netherlands, Poland, Slovenia, Spain, Sweden and the UK.

The cumulative cost was estimated for four frequent OCS-related comorbidities, *i.e.*, dyspepsia, hypertension, anxiety/depression and sleep disorder (for more details see, OCS usage among SA patients and OCS-related AEs). Annually, over 10 years, we assumed that new SA cases receiving OCS will develop the lowest rate and severity of OCS-related comorbidity [15], with the rate increasing, year on year, if patients remain on OCS. The model simulates various OCS sparing scenarios, in which a percentage of patients each year halts OCS use, and for them, the process of onset of OCS-related comorbidity is reversed.

For each country, calculations were carried out from their national healthcare system perspective, and no indirect costs were included. The costs of any asthma treatment (biologic and OCS) were not considered. The simulation was implemented and conducted using R version 4.3.0 (www.R-project.org/).

BIM input parameters

SA incidence and prevalence

The population data entering the model consisted of adults with newly or previously diagnosed SA but not treated with biologics (figure 1, supplementary table S.3). In each country, the number of SA patients was computed using SA epidemiological values reported by the 2021 national population statistics [21], from which the adult (over 18-year-old) estimated population size was derived. A pragmatic literature review was conducted to identify relevant national SA incidence and prevalence data (review results are presented in supplementary table S.1). It was evident that the SA incidence and prevalence values retrieved were incompatible. Upon detailed discussion with the SHARP CRC national leaders and chairs (EB; RD; EH; PK; RL; DRB; SS, BD; ZC, ATB; LH; AB) [22], it was agreed that in general, SA prevalence values were more plausible than the estimates of SA incidence. Prevalence values were therefore used to derive incidence values, by assuming a disease duration of 23 years. This approach led to a mean estimated incidence of 0.3%, consistent with findings from a previous study [23].

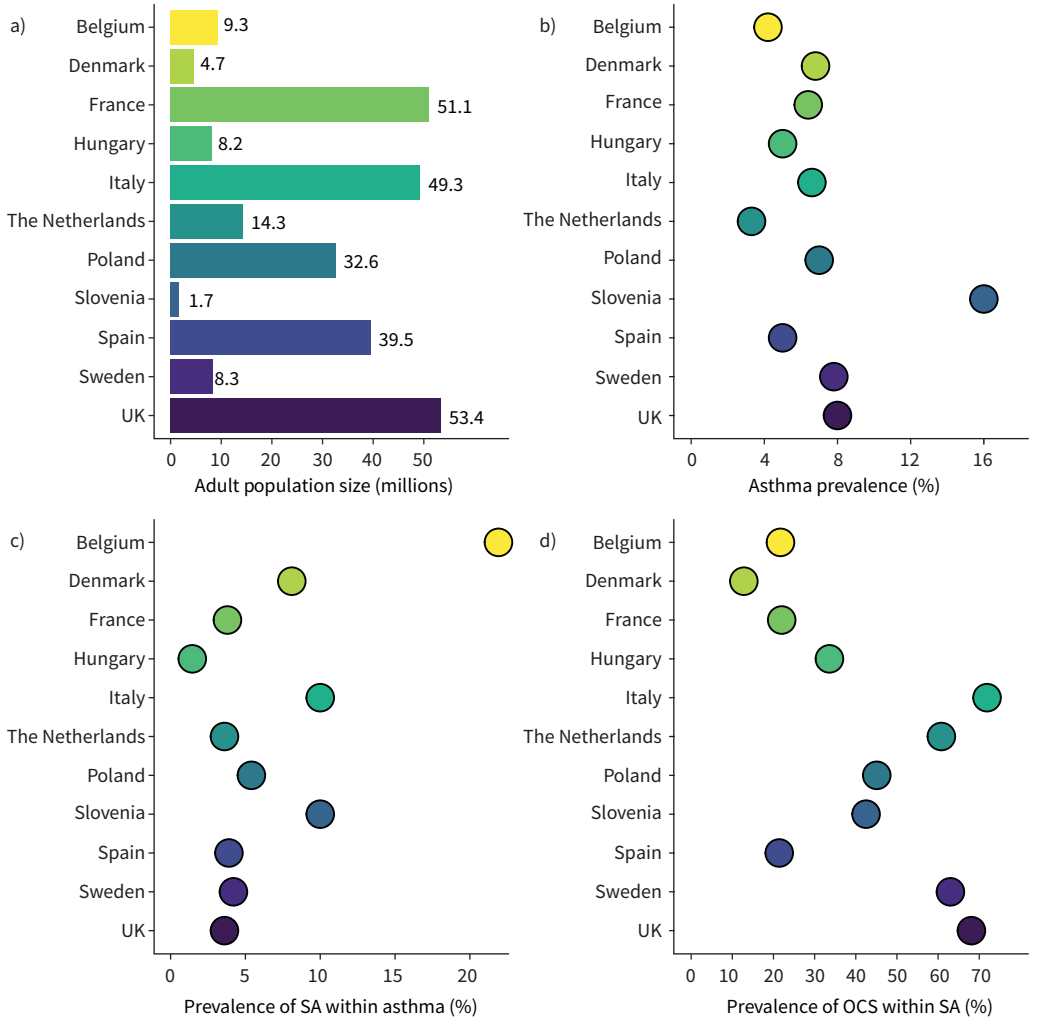


FIGURE 1 Budget impact model (BIM) input data. a) Bar plot of adult population size in the 11 countries considered. b) Mean asthma prevalence (%), by country. c) Mean prevalence of severe asthma (SA) within asthma (%), by country. d) Mean prevalence of maintenance oral corticosteroid (OCS) use within SA (%), by country.

OCS usage among SA patients and OCS-related AEs

The pragmatic literature search provided estimates of the prevalence of SA patients treated with maintenance OCS in each country (figure 1; supplementary table S.3).

Comprehensive country-specific data on the rates of AEs ascribable to exposure to systemic OCS are not available; therefore, the study by Sweeney *et al.* [15], based on a UK respiratory database, was used to inform the BIM. In the model, three risk categories were considered, with respect to exposure to OCS and estimated potential for OCS-related AE, as follows:

Risk category 1: SA patients not on OCS. The characteristics of the control non-asthmatic population of Sweeney *et al.* [15] were adopted for patients not receiving OCS.
Risk category 2: SA patients newly on OCS. The population with mild/moderate asthma in Sweeney *et al.* was used to model SA patients newly initiating OCS.
Risk category 3: SA patients on long-term OCS. AE prevalence from Sweeney *et al.* [15] SA population was used for patients on maintenance OCS.

While Sweeney *et al.* [15] considered the development of 12 different OCS-related conditions (type 2 diabetes, obesity, osteoporosis, fracture, dyspeptic disorders, glaucoma, cataract, cardiovascular disease, hypertension, psychiatric conditions/anxiety/depression, sleep disorder, chronic kidney disease), the present modelling exercise included only those that could be confidently considered fully reversable when

TABLE 1 Assumed annual incidence of reversible comorbidities related to oral corticosteroids (OCS) usage by risk category (adapted from Sweeney *et al.* [15])

Comorbidity	SA, not on OCS	SA, newly on OCS	SA, on long-term OCS
Dyspepsia	0.24	0.34	0.65
Hypertension	0.25	0.29	0.34
Psychiatric disorders	0.25	0.31	0.38
Sleep disorder	0.02	0.025	0.04

The first risk category (SA, not on OCS) represents the background level of risk. Upon initiating maintenance OCS, patients move into the second risk category (SA, newly on OCS) and eventually the third category with transition times of 1 year/2 years/3 years, according to the transition assumption. Upon halting OCS, the process reverses, with the same transition times. SA: severe asthma.

interrupting OCS usage. In the absence of published reversibility data, a survey was circulated among all the SHARP CRC National Leads and a consensus reached to include dyspepsia, psychiatric disorders, sleep disorders, hypertension and pneumonia in the model analysis (table 1). The survey and the results are described in supplementary material S.2.

Healthcare costs associated with the development and management of OC-related AEs

The healthcare costs pertaining to the management of the OCS-related AEs included in the model were extracted from published cost-of-illness studies (table 2) and expressed in euros (2021 rates) for each country. The incidence rate of pneumonia due to OCS usage in SA was not documented by Sweeney and colleagues [15] and could not be found in the literature; therefore, pneumonia was excluded from the current analysis. In the event of epidemiological and/or unit cost missing data for some AEs (dyspepsia in: Belgium, Denmark, Italy Poland, Slovenia, Sweden; hypertension in Slovenia), we used, as a benchmark, the costs retrieved for Spain, for which data were complete. All countries had at least partial cost data, so in the event of a missing value, the available cost data were compared between the country of interest and Spain, and a mean multiplier was derived to impute the missing value.

BIM scenarios

The BIM calculated the mean annual cost per patient for each of the three risk exposure groups, and this cost was applied to the national target populations for each country. In the BIM, the OCS-related shadow costs due to dyspepsia, psychiatric disorders, sleep disorders and hypertension were estimated assuming increasing risk of onset over the first years of OCS administration. In the 1-year model, SA patients initiating OCS treatment are assumed to experience the first (lowest) risk category for 1 year, followed by the second (higher) risk category for 1 year, and the third (highest) risk category thereafter. Upon stopping OCS, the process reverses, so the risk level drops down one category per year, over 3 years. The 2-year and 3-year models operate similarly, except that the transition times are 2 years or 3 years, respectively.

TABLE 2 Assumed annual costs of oral corticosteroid (OCS)-induced comorbidities, per patient (euros)

Country	Annual cost of OCS-induced comorbidities per patient (euros)			
	Dyspepsia	Hypertension	Psychiatric disorders	Sleep disorders
Belgium	1285[#]	649 [24]	9209 [25]	919 [25]
Denmark	777[#]	125 [26]	9883 [25]	976 [25]
France	361 [27]	537 [28]	8836 [25]	871 [25]
Hungary	9 [29]	606 [30]	4439 [25]	433 [25]
Italy	638[#]	272 [31]	1327 [25]	740 [25]
The Netherlands	939 [32]	258 [33]	10 051 [25]	1020 [25]
Poland	339[#]	736 [34]	4124 [25]	402 [25]
Slovenia	488[#]	247[#]	5689 [25]	576 [25]
Spain	495 [35]	250 [36]	2440 [37]	680 [37]
Sweden	1335[#]	193 [38]	8905 [25]	925 [25]
UK	605 [39]	420 [40]	11 600 [25]	1069 [25]

The source citation, where available, is provided in square brackets. [#]: values that were derived.

The "upper boundary scenario" (or "reference scenario") simulated the effects of daily OCS usage on the cost of OCS-AEs, over a 10-year time horizon, taking into account population size and country-specific estimates of the prevalence and incidence of the following: asthma, severe asthma, initiation of OCS, and onset and cost of each AE. The 10-year horizon was chosen to allow the effect of reduced OCS use to fully manifest.

This scenario was compared to a variety of OCS sparing situations in which different proportions of SA patients (75%, 50%, 25%) were assumed to halt OCS treatment each year. The halting of OCS led to stepwise transitions to lower AE risk categories over time, as described above.

Given the model's reliance on several assumptions, it is emphasised that the BIM outputs are intended to estimate the order of magnitude of the cumulative costs in each country, as opposed to the euro cost. Also, given the intrinsic differences among healthcare systems, the output should be evaluated country by country, and we discourage any benchmarking exercise.

BIM sensitivity analyses

Confidence intervals were generated by means of a multi-way sensitivity analysis. The following input parameters were allowed to vary: asthma prevalence, severe asthma prevalence within asthma, prevalence of OCS use within severe asthma and all AE risk parameters. For each parameter, a random binomial distribution was generated around the tabulated mean, and the latter was used to recalculate the parameter of interest. Different random binomial distributions were generated for each base simulation, each change in health status and each assumption regarding OCS sparing effect. A thousand simulations were conducted for each scenario, and confidence intervals were given by the 5th and 95th percentiles of the empirical distributions generated.

Results

For each country, the number of prevalent and incident asthmatic adult patients, the number of individuals with prevalent SA, the number of incident SA patients per year, and how many were treated with maintenance OCS were derived using the epidemiological values listed in supplementary table S.3. In the reference scenario, the model assumed that all patients remained on maintenance OCS for a period of 10 years, generating an annual cost per patient due to the four OCS-induced AEs. For illustrative purposes, in France, the modelled population included 3 272 816 asthmatic adults, 124 367 prevalent and 5407 incident SA patients per year, and 27 361 people were treated with maintenance OCS.

Figure 2 and table 3 depict the BIM modelled results, showing the national savings associated with OCS sparing scenarios in which 75%/50%/25% of SA patients remain on OCS while the remaining 25%/50%/75% are completely weaned off OCS. Results are further stratified according to whether the risk of comorbidities changes after 1, 2 or 3 years of treatment, respectively. Again, for illustrative purposes, in France, the 10-year national expenditure due to the management of OCS-related comorbidities was estimated at EUR 633.6 million for patients staying on OCS ("reference scenario") and EUR 517.0 million under a yearly 25% OCS sparing scenario, assuming the 1-year model of increasing risk. In this specific case, the model estimated national savings of EUR 116.6 million over 10 years. These results should be interpreted in terms of order of magnitude: a 25% sparing scenario, assuming 1 year to onset of comorbidity, produced savings of over 18% over 10 years.

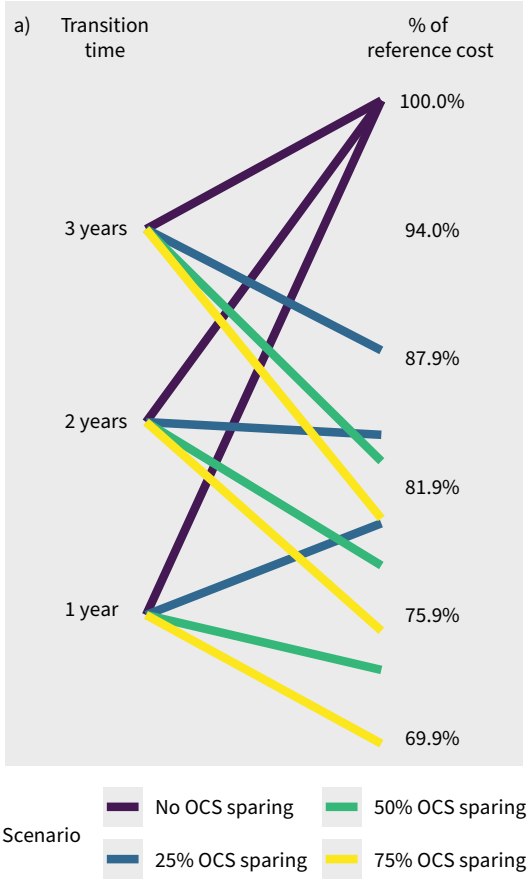
Looking across all scenarios, results show potential cost savings due to OCS sparing ranging from 11.7% to 30.1% arising out of an estimated reduction of OCS-related comorbidities over 10 years among SA patients. The magnitude of the saving depends upon the rate of onset of comorbidity, and the proportion of the population stopping OCS each year. In general, the BIM consistently estimates that the faster the rate of implementation of OCS sparing strategies, the higher the cost-offsets, as shown in figure 1. In each scenario simulated, and by design, there is strong consistency across countries in the percentage reduction of costs associated with OCS sparing.

Table 4 shows, *via* confidence intervals, the variability around the estimates of cost savings, allowing for error in the estimates of prevalence and risk.

Discussion

This study aimed to estimate the economic consequences of AEs ascribable to maintenance OCS use in SA patients, and thus to quantify the order of magnitude of avoidable costs. Ultimately our goal was to provide evidence of the potential health-economic benefit of equal access to efficient treatment options that improve asthma control, and are effective in reducing OCS dependency [41]. The costs of OCS-related

a)



b)

Simulated reference cost

Country	Cost million euros (95% CI)
Belgium	519 (493–545)
Denmark	88 (83–93)
France	634 (598–670)
Hungary	23 (22–25)
Italy	1472 (1422–1523)
The Netherlands	285 (270–301)
Poland	693 (660–727)
Slovenia	186 (176–196)
Spain	136 (130–142)
Sweden	454 (431–477)
UK	3173 (2993–3355)

FIGURE 2 a) Graphical display of the reduction in oral corticosteroid (OCS)-induced adverse event (AE) cost over 10 years, under various assumptions concerning transition to/from AE, and the extent of OCS sparing, per year. The three assumed transition times (1 year; 2 years; 3 years), are given by nodes on the left of the figure, and four assumptions of OCS sparing (0%; 25%; 50%; 75% of patients, per year) are colour-coded as shown in the legend. b) Reference cost (0% sparing), by country with 95% CI. These figures represent the 100% mark in a.

AEs have been estimated previously [9, 12, 42]; however, to our knowledge, our study is the first to estimate the disease-associated costs and potential benefits of OCS sparing strategies.

Using a budget impact model built on both evidence and hypotheses, our first important conclusion is that sparing OCS as early as possible is cost-effective, because most OCS-related AEs are poorly reversible and sometimes manifest as chronic comorbidities.

Our second important conclusion is that the estimated cost of our subset of OCS-related comorbidities ranges between EUR 23.3 million and EUR 3171.5 million by country over 10 years in the absence of OCS sparing. In general, OCS sparing strategies could reduce reversible AE costs by nearly a third over a 10-year horizon.

We acknowledge various limitations. In this article, we report on a subset of OCS-induced AEs considered "reversible", and we do not quantify important indirect economic costs pertaining to absenteeism, disability and lost productivity. We provide what is certain to be an underestimate of the true economic burden of OCS-induced AEs. More or less, our model found estimates that fit within the ranges reported in previous studies considered reliable for our purpose, as it was conducted during a period when biologics were not yet available [12].

Secondly, we observed wide variations in published costs and estimates of incidence/ prevalence, suggesting that under- and overdiagnosis biases may be present. We acknowledge our reliance on the work of Sweeney *et al.* [15] and the absence of complete and current data on healthcare systems, reimbursement

TABLE 3 Simulation results (millions of euros) over 10 years, under three assumptions of time to change in health status (transition time: 1 year; 2 years; 3 years), and three assumptions of oral corticosteroid (OCS) sparing (25%; 50%; 75% per year)

Country	1-year transition		2-year transition		3-year transition	
	OCS sparing, millions of euros	Delta	OCS sparing, millions of euros	Delta	OCS sparing, millions of euros	Delta
25% sparing						
Belgium	413.27	−105.51	427.46	−82.11	441.72	−60.69
Denmark	70.83	−17.09	73.20	−13.25	75.56	−9.73
France	516.99	−116.63	533.51	−90.06	549.94	−65.78
Hungary	19.31	−4.02	19.90	−3.09	20.48	−2.24
Italy	1119.94	−351.30	1163.26	−276.67	1207.72	−208.12
The Netherlands	228.99	−56.13	236.70	−43.55	244.41	−32.04
Poland	562.01	−130.40	580.08	−101.04	598.12	−74.18
Slovenia	149.57	−36.12	154.55	−28.01	159.53	−20.59
Spain	106.92	−28.89	110.70	−22.57	114.53	−16.77
Sweden	359.29	−94.11	371.87	−73.31	384.53	−54.25
UK	2576.63	−594.91	2660.30	−459.91	2743.61	−336.48
50% sparing						
Belgium	376.74	−142.04	395.44	−114.13	414.91	−87.49
Denmark	64.90	−23.03	68.00	−18.45	71.22	−14.07
France	476.38	−157.24	497.98	−125.59	520.37	−95.34
Hungary	17.91	−5.42	18.67	−4.32	19.46	−3.26
Italy	999.36	−471.88	1057.31	−382.61	1118.16	−297.68
The Netherlands	209.52	−75.60	219.64	−60.61	230.16	−46.29
Poland	516.72	−175.69	540.42	−140.70	565.03	−107.27
Slovenia	137.03	−48.66	143.57	−38.99	150.36	−29.75
Spain	96.94	−38.86	101.95	−31.31	107.18	−24.12
Sweden	326.72	−126.68	343.32	−101.85	360.61	−78.17
UK	2369.66	−801.89	2479.17	−641.05	2592.74	−487.35
75% sparing						
Belgium	358.39	−160.39	379.49	−130.08	401.10	−101.31
Denmark	61.91	−26.02	65.40	−21.05	68.97	−16.32
France	455.91	−177.70	480.14	−143.43	504.91	−110.80
Hungary	17.20	−6.13	18.05	−4.94	18.92	−3.80
Italy	939.08	−532.16	1005.15	−434.78	1073.00	−342.84
The Netherlands	199.72	−85.40	211.12	−69.13	222.77	−53.67
Poland	493.93	−198.48	520.58	−160.54	547.84	−124.47
Slovenia	130.72	−54.97	138.08	−44.48	145.60	−34.51
Spain	91.94	−43.87	97.61	−35.66	103.42	−27.88
Sweden	310.37	−143.03	329.11	−116.06	348.30	−90.48
UK	2265.42	−906.12	2388.34	−731.87	2514.02	−566.07

policies and access to biologics. There are gaps in the literature both for cost and epidemiological data, where further research is needed. We emphasise the order of magnitude of percentage savings, as opposed to absolute numbers.

Thirdly, susceptibility to OCS-related AEs is heterogeneous due to multiple cofactors. For example, the risk of osteoporosis is influenced by sex, diet and age, features of which may vary strongly throughout Europe. The risk of adrenal insufficiency can be influenced by genetic predisposition [43], which may vary in frequency among countries. It is highly likely that some comorbidities may not be considered directly related to OCS exposure but, instead, are blurred in the cascade of events associated with OCS exposure, such as obesity, depression, sleep disorders and later vascular events.

Lastly, although it is well established that SA patients are more susceptible to comorbidities [15], most of the steroid-induced comorbidities seen in severe asthma may be partly attributable to exposure to corticosteroids given by other routes (inhaled, intranasal, skin creams, periarticular infiltration, *etc*.).

Despite these issues and simplifications, modelling studies are important and necessary. The only alternative is a randomised clinical trial with long-term follow-up, which would be ethically indefensible. The

TABLE 4 Per cent cost saving due to four oral corticosteroid (OCS)-related comorbidities, under nine scenarios

Transition times	Cost saving % (95% CI)		
	25% OCS sparing	50% OCS sparing	75% OCS sparing
5-year model timespan			
1-year	12.1 (9.4–15.0)	19.5 (15.4–24.2)	24.3 (19.3–29.6)
2-year	6.2 (4.3–8.1)	10.7 (7.7–13.9)	13.9 (10.3–17.8)
3-year	3.0 (1.8–4.1)	5.4 (3.5–7.4)	7.3 (4.8–9.9)
10-year model timespan			
1-year	19.7 (15.7–24.1)	26.7 (21.2–32.4)	30.0 (24.0–36.5)
2-year	15.6 (12.3–19.4)	21.8 (17.1–26.8)	24.7 (19.6–30.4)
3-year	11.6 (8.8–14.8)	16.9 (13.0–21.1)	19.5 (15.2–24.3)

Data are reported for a 5-year and a 10-year BIM timespan. 95% CI values were derived by simulating risk and prevalence values under a binomial model.

informativeness of historical comparisons is diminished by significant changes over time, in healthcare systems and our levels of understanding of OCS-induced comorbidities. Pre and post OCS sparing comparisons have been reported in the literature, but they are always short-term and carry their own limitations. In particular, very few physicians stop treating OCS-related conditions such as diabetes, hypertension or osteoporosis. Cataract can be surgically treated once severe, but the paradox is that from an economic – not a patient – perspective, the best scenario is to suffer from a cataract severe enough to become surgically accessible. From a patient perspective, near-blindness is endured, and not all fully recover after surgery.

Our results strongly advocate for earlier intervention before patients enter the vicious cycle of OCS exposure. It was recently shown that just one-off prescription of OCS can lead to significant – certainly limited – increased risk of OCS-induced comorbidity [44], and that the probability of transitioning to frequent prescription was higher in patients with pre-existing risk factors for OCS-induced comorbidities such as obesity, female sex or smoking.

The benefits of OCS sparing drugs are well-established and shared by all SA stakeholders, and they reflect a patient perspective in terms of important outcomes, such as quality of life, exacerbation rates, symptoms and lung functions. This does not require additional evidence. No clear quality-adjusted life-year and disability-adjusted life-year studies have been conducted so far that provide new information in this regard. What is evident from our modeling study is that every year of delay represents a missed opportunity.

The findings in our study provide clear support for the view that the best strategy for limiting both the patient and the economic burden of OCS-induced comorbidities is early intervention, before OCS comorbidities become manifest.

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