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To cite this article: Jonas Daugherty, Xiwu Lin, Richard Baxter, Robert Suruki & Eric Bradford (2017): The impact of long-term systemic glucocorticoid use in severe asthma: A UK retrospective cohort analysis, Journal of Asthma, DOI: [10.1080/02770903.2017.1353612](https://doi.org/10.1080/02770903.2017.1353612)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1353612>



Published online: 19 Sep 2017.



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The impact of long-term systemic glucocorticoid use in severe asthma: A UK retrospective cohort analysis

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ABSTRACT

Objective: Systemic glucocorticoids (SGCs) are a treatment option for severe asthma but are associated with the development of adverse events (AEs). Evidence on the extent of SGC use and the relationship between SGC dose and AE risk in severe asthma is limited. **Methods:** Patients with severe asthma (Global Initiative for Asthma step 4/5), with no SGC use during the <6–12 months before severe asthma determination (index date) were identified in the UK-based Clinical Practice Research Datalink database (2004–2012). Patients were assessed for SGC exposure and an incident diagnosis of an SGC-related AE (cataracts, diabetes, myocardial infarction [MI], osteoporosis, peptic ulcer or stroke) during the 8-year observation phase. The dose-related risk of an SGC-related AE was determined using AE-specific Cox proportional hazards models. **Results:** Overall, 75% of 60,418 patients identified with severe asthma received SGC during the 8-year follow-up, with the majority receiving an average of >0–≤2.5 mg/day. The risk of diabetes (hazard ratio [HR]: 1.20 [95% confidence interval (CI): 1.11, 1.30]), MI (HR: 1.25 [95% CI: 1.09, 1.43]) and osteoporosis (HR: 1.64 [95% CI: 1.51, 1.78]) was increased at low SGC doses (0–2.5 mg/day), with further risk increases at doses >2.5 mg/day versus no SGC use. Compared with no SGC use, SGC increased the risk of peptic ulcer in a non-dose-dependent manner, but the risk of stroke was unchanged. **Conclusions:** Most patients with severe asthma are exposed to SGC, which increases SGC-related AE risk. This suggests that SGC exposure should be minimized as recommended by asthma treatment guidelines.

ARTICLE HISTORY

Received 5 May 2017

Revised 3 July 2017

Accepted 5 July 2017

KEYWORDS

Adverse event; claims database; diabetes; myocardial infarction; oral glucocorticoids; osteoporosis; cataracts; pharmacology; peptic ulcer; stroke

Introduction

Asthma is a chronic airway disease characterized by bronchial constriction and airway inflammation [1]. The severity of asthma varies across patients, with 5–10% of patients with asthma estimated to have severe asthma [2]. Severe asthma is characterized by poor symptom control and frequent exacerbations despite the regular intensive use of maintenance therapies such as inhaled glucocorticoid (IGC) and long-acting bronchodilators [2]. The inability of these patients to achieve adequate asthma control with these maintenance therapies often necessitates the use of systemic glucocorticoids (SGC) as acute and chronic add-on therapy [1,3]. Evidence from clinical registries and randomized clinical trials suggest that 10–50% of patients with severe asthma have received treatment with SGC, with an average dose of 10–15 mg/day at the time of study enrollment [4–10]. This is greater than the ≤7.5 mg/day of SGC recommended

by the Global Initiative for Asthma (GINA) guidelines suggesting that these patients are not achieving adequate control at guideline-recommended doses [1].

The chronic use of SGC in diseases such as asthma, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) has been associated with the development of a range of adverse events (AEs), with some of the most frequent including cataracts, diabetes, peptic ulcers, cardiovascular disease (CVD), cerebrovascular events and osteoporosis [11–18]. In general, these SGC-related comorbidities increase the burden of disease for patients and healthcare providers, with SGC use being associated with lower patient quality of life, increased healthcare resource utilization and high economic costs for patients [11, 14, 16].

As the majority of studies characterizing SGC use and the risk of AEs are from patients with non-asthma conditions, a recent publication by Choo and Pavord 2016

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has called for this relationship to be further characterized in a severe asthma population [19]. This is important as patients with severe asthma have different comorbidities and demographic characteristics to other disease populations [12, 20]. Specifically, the risk of SGC-related AEs and the relationship between individual AEs and SGC dose in patients with severe asthma require further investigation. The primary objectives of this study were to characterize the use of SGC and to determine the effect of SGC use on the incidence and risk of key SGC-related AEs in a UK population-based cohort of patients with severe asthma.

Methods

Study design

This was a retrospective, longitudinal cohort study using electronic medical records from the UK-based Clinical Practice Research Datalink (CPRD) database (January 1, 2004 to March 31, 2012). The CPRD contains de-identified patient data from a general practitioner setting from across the United Kingdom. For patients in practices located in England, records were linked to Hospital Episode Statistics (HES), containing records of National Health Service hospital admissions, hospital-based outpatient appointments, and accident and emergency (A&E; emergency room) visits. Data was extracted for patients with severe asthma [1].

The study consisted of three time phases: the look-back phase, the baseline phase and the observation phase (Figure 1). The index date for each patient was the date that the patient was identified as having severe asthma (GINA step 4/5) [1] based on prescribing information in their primary care record; this marked the start of the observation phase. During the look-back phase (12–6-month period prior to the index date), patients were established as new SGC users; only patients with no SGC use during this phase were included in the study. During the baseline phase (6–0 months prior to the index date), a patient’s status as a new SGC user was assessed and SGC use was permitted. Following the index date, patients were observed for a variable period of time (observation phase)

until an incident (first) event of an AE of interest, the end of the study period, transfer out of a participating CPRD practice or death.

Patients

Eligible patients were ≥18 years of age at the index date; met the definition of severe asthma (GINA step 4: receiving medium- or high-dose inhaled corticosteroid [ICS] and long-acting β₂ agonist or high-dose ICS and leukotriene or theophylline or GINA step 5: add-on therapy with anti-immunoglobulin E or low-dose oral glucocorticoids, in addition to step 4 treatment [1]) during the pre-index phase; had an index date between January 1, 2004 and March 31, 2012; and were registered in an English practice with linked HES data during the 12 months prior to the index date and until end of patient assessment, transfer out of a participating CPRD practice or death. There was no requirement for a minimum follow-up period. Exclusion criteria were a diagnosis of respiratory cancer or intrathoracic cancer during the observation period, or at any time in the patient’s history a diagnosis of cystic fibrosis, a diagnosis of autoimmune disease or a medical history of organ transplantation.

Outcomes and assessments

Definition of SGC exposure

SGC exposure during the observation phase was measured using data from SGC prescriptions, including days of supply and dosage. Outpatient oral SGC prescriptions were identified using CPRD product codes (see supplementary methods). SGC dose was estimated as the quantity dispensed multiplied by the SGC dose per dosage unit. Where these data were not available, the number of days’ supply was estimated using patterns from prior patient records for the same drug, strength and quantity. If these data were not available, an expert opinion-derived algorithm was used (Supplementary methods). Patients with no SGC use were defined as those with no SGC exposure during both the baseline and observation phases.

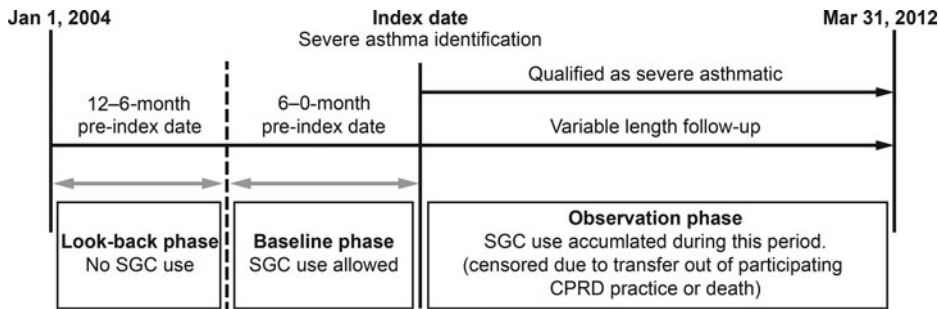


Figure 1. Study design diagram. The baseline and observation phases were subdivided into 28-day periods over which SGC use was assessed. CPRD, Clinical Practice Research Datalink; SGC, systemic glucocorticoid.

As therapies are not recorded in the HES, SGC administration after asthma-related A&E visits or hospitalizations (indicated by asthma medical codes) were estimated using algorithms based on asthma treatment guideline recommendations [3, 21, 22]. An average dose of 125 mg methylprednisolone (prednisolone 156 mg equivalent) was added to a patient's SGC exposure for each asthma-related A&E visit [23]. Following discharge for an asthma-related A&E visit, an average dose of 200 mg prednisolone (5 days at 40 mg/day) equivalent was added to patient SGC exposure if no SGC administration was noted post-discharge [21, 22]. If a patient was admitted to a hospital, an average dose of 60 mg methylprednisolone (prednisolone 75 mg equivalent) was added to a patient's SGC exposure for each day of inpatient asthma treatment [21].

To account for differing SGC routes of administration and dosage forms, SGC exposure was converted to equivalent prednisolone strength units based on a conversion table (Table S1). Any ICS use was not included due to its lower and more inconsistent bioavailability compared with SGC. For a given 28-day period of interest, the average daily SGC dose (any dose) was calculated as the total SGC dose in milligrams since the 6 months prior to the index date to the time of interest, divided by the total number of days of patients observation during the same time period.

Adverse events

AEs were assessed by an incident diagnosis (first record of the event after the index date) of the most frequent predefined AEs, known to be SGC-related [11–18] (cataracts, type 2 diabetes, myocardial infarction [MI; acute MI regardless of patient survival], osteoporosis [including use of drugs to treat osteoporosis], peptic ulcer [peptic or gastric ulcer] or stroke [occlusive or hemorrhagic stroke regardless of survival]) in patients without an event during the look-back and baseline phases. An incident diagnosis of an AE was determined from patient medical records (CPRD: Read codes; HES: International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes) (supplementary methods). For each individual AE, the incidence rate of AEs during the observation phase, the risk (hazard ratio [HR]) of SGC-related AEs and the dose-related risk of SGC-related AEs compared with non-SGC use was determined.

Statistical analysis

Patient characteristics (age, gender, GINA step and weight) were identified at the index date (date of severe asthma identification). Categorical variables were reported as frequencies and proportions, and continuous variables as mean (standard deviation [SD]). Based

on discussion with clinical experts, SGC exposure over time was analyzed by average daily dose (none, $>0\text{--}\leq 2.5$, $>2.5\text{--}\leq 5$, $>5\text{--}\leq 7.5$ and >7.5 mg/day) and SGC exposure split into 28-day increments to account for variations in dosage. AE incidence rates with 95% confidence intervals (CIs) were reported as the rate per 1000 person-(28 day)-periods. Patients with an AE of interest during the look-back and baseline phases or at their index date were excluded, and only the first incidence of an AE was included in the analysis.

The dose-related risk of AEs was assessed by Cox proportional hazards model using daily SGC dose segments (none, $>0\text{--}\leq 2.5$, $>2.5\text{--}\leq 5$, $>5\text{--}\leq 7.5$ and >7.5 mg/day) as a variable, with no SGC use as the reference category. Dose-range HRs were compared using multiple comparisons, adjusted by the Tukey–Kramer method [24]. If no statistically significant differences between contiguous daily dose ranges were identified, ranges were combined into new dose ranges and new comparisons made. Dose-range cut-off points were confirmed if contiguous dose ranges demonstrated statistical non-equivalence.

The risk (HR) of SGC-related AEs was assessed using AE-specific Cox proportional hazards models with time-varying covariates and exposure. To account for chronic and acute SGC exposures during the observation phase, average cumulative SGC dose up to the 28-day period of data sampling and the SGC dose during the 28-day period before data sampling were both included in each model as key SGC predictor variables. For each AE model, non-SGC risk factors known to affect the development of AEs were also included if they were not collinear with other non-SGC risk factors and were considered potential confounders between SGC doses and AEs. Individual predictors potentially endogenous with other predictors (e.g., gender) were not permitted to vary over the duration of the observation phase (Table S2). Data were reported as adjusted HR with 95% CIs separately for average cumulative SGC dose per day and average daily SGC dose for prior 28-day period before the period of data sampling.

Results

Study population characteristics

A total of 60,418 patients with severe asthma were identified in the UK CPRD. Of these, 24,994 (41%) did not receive SGC treatment during the baseline and observation phases. SGC users tended to be older, and were predominantly female and non-smokers compared with non-SGC users (Table 1).

SGC exposure over time

Approximately 74% of the 60,418 patients with severe asthma included in the study observation phase had not

Table 1. Demographics and clinical characteristics at screening (overall cohort).

Variable	No SGC use	SGC user	Overall
Total number of patients, <i>N</i> (%) ^a	24,994 (41.4)	35,424 (58.6)	60,418
Age (years), mean (SD)	51.50 (18.7)	54.77 (17.6)	53.42 (18.1)
Age, <i>n</i> (%)			
18–34	5401 (21.6)	5257 (14.8)	10 658 (17.6)
35–44	4467 (17.9)	5642 (15.9)	10 109 (16.7)
45–54	4051 (16.2)	5851 (16.5)	9902 (16.4)
55–64	4040 (16.2)	6887 (19.4)	10 927 (18.1)
65+	7035 (28.2)	11 787 (33.3)	18 822 (31.2)
Female, <i>n</i> (%)	14,476 (57.9)	22,861 (64.5)	37,337 (61.8)
Smoking status, <i>n</i> (%)			
Non-smoker	17,170 (68.7)	10,631 (66.3)	40,672 (67.3)
Smoker	5035 (20.1)	3351 (21.4)	12,606 (20.9)
Unknown status	2789 (11.2)	1941 (12.3)	7140 (11.8)
BMI (kg/m ²), <i>n</i> (%)			
Underweight (0–<18.5)	268 (1.1)	152 (1.0)	633 (1.1)
Normal (18.5–<25)	3573 (14.3)	2065 (12.5)	8016 (13.3)
Overweight (25–<30)	4375 (17.5)	2549 (15.7)	9943 (16.5)
Obese (≥30)	4687 (18.8)	3265 (20.4)	11 913 (19.7)
Missing	12,091 (48.4)	7892 (50.3)	29,913 (49.5)
GINA treatment step 5, <i>n</i> (%)	21 (0.1)	6364 (43.7)	15,490 (25.6)
Years of follow-up, mean (SD)	3.08 (2.3)	4.37 (2.4)	3.83 (2.4)
Years of follow-up, <i>n</i> (%)			
<1	3195 (12.8)	1574 (4.4)	4769 (7.9)
≥1–<2	4982 (19.9)	3682 (10.4)	8664 (14.3)
≥2–<3	4040 (16.2)	4079 (11.5)	8119 (13.4)
≥3–<4	3266 (13.1)	4502 (12.7)	7768 (12.9)
≥4–<5	2625 (10.5)	4447 (12.6)	7072 (11.7)
≥5–<6	2224 (8.9)	4348 (12.3)	6572 (10.9)
≥6–<7	1884 (7.5)	4373 (12.3)	6257 (10.4)
≥7–<8	1629 (6.5)	4463 (12.6)	6092 (10.1)
≥8	1149 (4.6)	3956 (11.2)	5105 (8.5)

Notes. ^aAs a proportion of the total group category; proportions are presented as a % of groups categories. BMI, body mass index; GINA, Global Initiative for Asthma; SGC, systemic glucocorticoid use; SD, standard deviation.

received SGC during the previous year. At the end of the approximately 8-year (mean of 3.83 years per patient) observation phase, there were 6004 patients left, 75% of whom had received SGC (Table 2). The proportion of patients exposed to an average cumulative SGC dose of 0–≤2.5 mg/day increased with each study observation year and was highest in the final observation year compared with other years, indicating that the majority of patients with severe asthma were exposed to SGC (Table 2). Only 3–4% of patients received an average

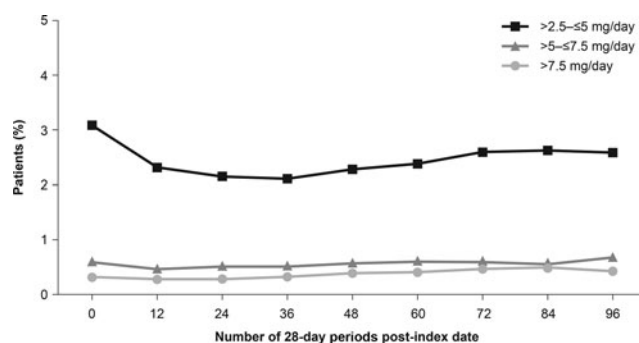


Figure 2. Average cumulative daily SGC exposure^a over time (overall cohort). Each period corresponds to 28 days. ^aAverage cumulative daily dose at the start of each set of 12, 28-day periods. Cumulative dose includes the average daily dose from the baseline phase 0–<6 months before the index date. SGC, systemic glucocorticoid.

cumulative SGC dose >2.5 mg/day at the beginning of each 28-day period, with this proportion remaining stable over time (Figure 2).

Incidence of SGC-related AEs

The most frequent SGC-related AE during the observation phase was cataracts (1.26 events per 1000 person-[28 day]-periods), followed by osteoporosis (1.13 events per 1000 person-periods) and diabetes (1.04 events per 1000 person-[28 day]-periods) (Figure 3). For MI, peptic ulcer and stroke, the incidence of events was 0.33–0.39 events per 1000 person-(28 day)-periods.

Dose-related risk of an SGC-related AE

Contiguous SGC dose-ranges were tested until statistical non-equivalence was demonstrated as shown in Table S3. The final dose-ranges showed that even at low doses of SGC (>0–≤2.5 mg/daily) compared with non-SGC users, the risk of developing diabetes (HR: 1.20 [95% CI: 1.11, 1.30]), MI (HR: 1.25 [95% CI: 1.09, 1.43]) and

Table 2. Average cumulative daily SGC dose over time during the observation phase (overall cohort).

No. of cumulative 28-day periods of observation	1–12	13–24	25–36	37–48	49–60	61–72	73–84	85–96	97–108
Total no. of patients remaining in study	60,418	52,227	44,363	37,024	29,726	23,409	17,299	11,576	6004
Average cumulative daily SGC dose ^a (mg/day)	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b	<i>n</i> (%) ^b
0	44,896 (74.3)	31,475 (60.3)	22,754 (51.3)	16,569 (44.8)	11,807 (39.7)	8342 (35.6)	5501 (31.8)	3298 (28.5)	1520 (25.3)
>0–≤2.5	13,122 (21.7)	19,158 (36.7)	20,311 (45.8)	19,371 (52.3)	16,967 (57.1)	14,283 (61.0)	11,168 (64.6)	7857 (67.9)	4263 (71.0)
>2.5–≤5.0	1853 (3.1)	1204 (2.1)	949 (2.1)	783 (2.1)	675 (2.3)	556 (2.38)	448 (2.6)	302 (2.6)	156 (2.6)
>5.0–≤7.5	358 (0.6)	247 (0.5)	224 (0.5)	185 (0.5)	167 (0.6)	136 (0.6)	101 (0.6)	64 (0.6)	40 (0.7)
>7.5	189 (0.3)	143 (0.3)	125 (0.3)	116 (0.3)	110 (0.4)	92 (0.4)	81 (0.5)	55 (0.5)	25 (0.4)

Notes. ^aAverage cumulative daily dose at the start of each set of 12, 28-day periods. Cumulative dose includes the average daily dose from the baseline phase 0–<6 months before the index date. ^bProportion of patients remaining at the period of observation. SGC, systemic glucocorticoid.

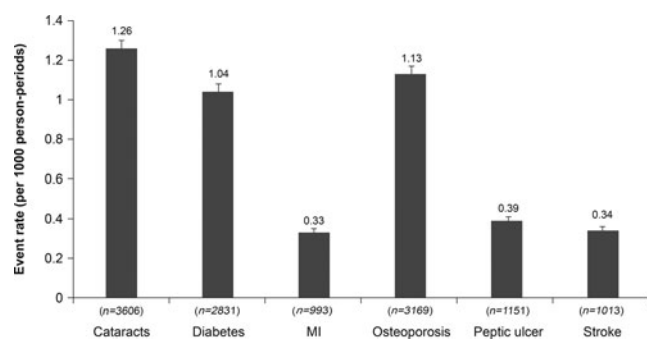


Figure 3. Overall incidence rate of SGC-related AEs during the observation phase (overall cohort). Patients with an AE of interest before the index were not included in the calculation; the exposure (any SGC dose) duration for patients with an AE of interest during the observation phase was the time from the index date to the date of the first incidence of an AE. One period consists of 28 days. AE, adverse event; MI, myocardial infarction; SGC, systemic glucocorticoid.

osteoporosis (HR: 1.64 [95% CI: 1.51, 1.78]) was significantly increased (Table 3). With average daily doses of SGC >2.5 mg, the risk of these AEs was further increased. The risk of cataracts was significantly increased with average daily doses of SGC >2.5 mg compared with no SGC use (Table 3), but not with lower doses of SGC. SGC use increased the risk of developing a peptic ulcer compared with no SGC use, although no dose-response relationship was demonstrated. The relative risk of developing a stroke was not significantly increased with SGC use compared with no SGC use (Table 3).

Table 3. Risk of developing SGC-related AEs by SGC dose range compared with non-SGC use – final dose segments (overall cohort).

AE	Average dose range (mg/day)	Adjusted hazard ratio (95% CI)	p-Value
Cataracts	0	Ref.	
	0–≤2.5	1.07 (1.00, 1.15)	0.052
	2.5 <–≤7.5	1.76 (1.52, 2.04)	<0.0001
Diabetes	>7.5	3.38 (2.41, 4.73)	<0.0001
	0	Ref.	
	0 <–≤2.5	1.20 (1.11, 1.30)	<0.0001
Myocardial infarction	>2.5	1.70 (1.44, 2.01)	<0.0001
	0	Ref.	
	0–≤2.5	1.25 (1.09, 1.43)	0.0012
Osteoporosis	>2.5	2.15 (1.67, 2.77)	<0.0001
	0	Ref.	
	0–2.5	1.64 (1.51, 1.78)	<0.0001
Peptic ulcer	2.5–5	6.79 (5.98, 7.73)	<0.0001
	>5	12.61 (10.45, 15.21)	<0.0001
	0	Ref.	
Stroke	>0 ^a	1.13 (1.00, 1.28)	0.0486
	0	Ref.	
	>0 ^a	1.11 (0.97, 1.27)	0.1253

Notes. See Table S2 for a list of the confounders each model was adjusted for.

^aNo significant differences in dose segments were found, so all the dose segments are combined into one single segment (SGC user) for peptic ulcer and stroke.

AE, adverse event; CI, confidence interval; SGC, systemic glucocorticoid.

Risk of an SGC-related AE

The risk of an SGC-related AE associated with a 5 mg/day increase in SGC dose during the 28-day period before the period of data sampling is shown in Table S4. The average cumulative dose is also shown in the table.

Discussion

The chronic use of SGC in a variety of conditions has been associated with the development of a range of AEs; however, most studies were performed in non-asthma conditions. Further investigation of the relationship between SGC use and dosage and development of SGC-related AEs was thus warranted. This study aimed to evaluate the impact of chronic SGC treatment in severe asthma and demonstrated that the majority of patients with severe asthma in this UK-based study were exposed to low average daily doses of SGC. However, even at these low average doses, the risk of AEs was significantly increased, with the dose-dependent risk of SGC-related AEs including cataracts, diabetes, MI and osteoporosis all increasing with SGC exposure.

Approximately three-quarters of patients with severe asthma were exposed to SGC during the 8-year observation phase. This was increased from the 26% who were exposed to SGC at the start of the study, a figure which may have partially been driven by the requirement that patients be new SGC users during the <6–12 months before index date. However, relatively few patients (<4%) received average SGC doses in excess of prednisolone 2.5 mg equivalent per day. This low average SGC dose is consistent with prior work in the United States using the Optimum Patient Care Research Database, which demonstrated that patients with severe asthma are exposed to a median daily dose of 5 mg prednisolone [12]. However, the SGC doses reported in the current study were lower than those reported in several clinical registry studies of patients with severe refractory asthma, receiving an average SGC dose of 15 mg/day at study entry [6, 7]. Furthermore, in patients with severe eosinophilic asthma, SGC doses of 10–15 mg/day have been reported at trial enrollment [8–10]. The lower SGC doses reported in the current study compared with previous studies may be partially attributable to the patient populations studied. In particular, in the current study, severe disease classification was based on having received GINA step 4/5 treatment, whereas in randomized clinical trials, patients are commonly required to meet further criteria to be classified as severe (e.g., a history of recent exacerbations) [4, 5, 9, 10]. Consequently, the patients in the current study may represent a less severe asthma population than in clinical trials. Overall, these results suggest that SGC use is higher than

the 0.9% use reported in the general (non-asthma) population [25], and that a small subset of the severe asthma population may not be achieving adequate symptom control with guideline-recommended SGC doses [1].

The dose–response relationship between SGC dose and the risk of AEs in the current study appeared to be specific for individual AEs and non-linear. With the exception of peptic ulcer and stroke, the risk of SGC-related AEs increased with increasing SGC dose, with cataracts, diabetes and osteoporosis being the most frequent events. The risk of peptic ulcer was increased with SGC use but demonstrated no dose–response relationship. Even at low doses (average: >0 – ≤ 2.5 mg/day), the risk of diabetes, MI and osteoporosis was increased 1.20- to 1.60-fold compared with no SGC use. Further increases in SGC dose beyond 2.5 mg/day did not increase the risk of diabetes or MI, but did increase the risk of osteoporosis (> 5 mg/day) and cataracts (> 7.5 mg/day). However, it should be noted that relatively few patients received SGC doses in excess of 2.5 mg/day, reducing the accuracy of results at higher doses of SGC. Nevertheless, these results are broadly consistent with several other studies, which have demonstrated an association between SGC use and AEs in a range of diseases including asthma, RA and SLE [11–18], and that the risk of several AEs including cataracts and MI is dose-dependent [26, 27]. In particular, a previous study by Sweeney et al. [12] demonstrated that the odds of developing cataracts, type 2 diabetes, CVD, dyspeptic disorders and osteoporosis was increased up to 5-fold in patients with severe asthma receiving a median of 5 mg SGC daily, compared with patients with mild-to-moderate asthma receiving a median 0 mg SGC daily. Similarly, Lefebvre et al. [11] also demonstrated that in patients with severe asthma, the risk of bone/muscle, cardiovascular, metabolic and ocular complications increased at SGC doses of 6–12 mg/day compared with ≤ 6 mg/day. However, increases in SGC dose in excess of 12 mg only resulted in small additional increases in the risk of these complications [11]. Together, this suggests that the risk associated with SGC use should not be generalized and is specific for individual AEs.

In accordance with AEs having specific SGC-related risks, the current study demonstrated no association between SGC exposure and an increased risk of stroke. Previous studies have also failed to consistently demonstrate a link between SGC use and stroke [16, 18, 28, 29]. In RA and SLE, a trend for an increase in the risk of stroke with SGC use has been demonstrated [18, 29]. However, a recent literature review showed no association between SGC use and stroke in patients with RA [28]. Furthermore, Souverein et al. [18] showed that the current use of SGC decreased the risk of stroke by approximately

10% in patients with chronic obstructive pulmonary disease (COPD) and RA. When the risk of stroke was assessed in each disease individually, the current use of SGC decreased the risk of stroke in patients with COPD but was increased in patients with RA. Overall, this suggests that SGC use and the risk of stroke may be disease-dependent.

The increased risk of AEs associated with SGC use may increase disease burden even at low doses, and suggests that SGC exposure should be minimized. This relationship is highly clinically significant as low-dose SGC use (< 7.5 mg/day) is recommended by the GINA guidelines in patients with severe asthma not achieving symptomatic control on alternative maintenance therapies [3]. This suggests a need for further comorbidity screening in patients receiving SGC therapy, in addition to a need to develop new therapeutic options for these patients. Additionally, new biologics have demonstrated the ability to reduce SGC use with a favorable benefit/risk profile, and should be readily considered when patients meet the required eligibility criteria, as recommended by asthma treatment guidelines [1, 8, 30–32].

A limitation of the current study is that asthma guidelines classify patients using chronic SGC treatment as having asthma at GINA step 5, but the design of the current study required patients to be new users of SGC. This may have restricted the enrollment of patients at GINA step 5 with chronic SGC use during the asthma classification (look-back phase). Also, the study analysis only considered the first incident diagnosis of an SGC-related AE, which may have led to an underestimation of the AEs that are often recurrent, in particular MI, peptic ulcer and stroke [33, 34]. Other AEs that tend to only be reported once per patient including cataracts, diabetes and osteoporosis are less likely to be affected by the study design. It is also important to acknowledge that there are potential issues with the recording of data in the CPRD, including patient conditions not being captured, patients with pre-existing conditions being missed and patient lifestyle changes. Additionally, the CPRD only indirectly records SGC exposure via primary care prescriptions and HES does not track drug use while in the hospital. Consequently, actual treatment use could not be determined, which may have led to AE risk being over- or underestimated. Finally, there is the potential for unmeasured confounding, as variables not included in the relative risk models may have contributed to the development of AEs. Strengths of this study include the use of expert developed algorithms to mitigate instances of missing data; in particular, SGC use and dosage were imputed when absent from patient medical records. This minimized the effect of missing data on the results.

Conclusion

This study demonstrated that the majority of patients with severe asthma are exposed to SGC at a low average dose, and SGC use increases the risk of cataracts, diabetes, peptic ulcer, MI and osteoporosis. These results suggest that if SGC is required, SGC doses should be as low as possible to achieve clinical effects and that the chronic use of SGC should be minimized, as recommended by asthma treatment guidelines.

CPRD

This study is based in part on data from the CPRD GOLD database obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the author/s alone.

Acknowledgements

The authors wish to thank Alex Lowe, PhD, from Fishawack Indicia Ltd, UK who provided editorial support with developing this manuscript (in the form of writing assistance, including development of the initial outline and draft based on author input, assembling tables and figures, collating authors comments, grammatical editing and referencing), funded by GSK.

Declaration of interest

JD was an employee of GSK during the conduct of the study and is currently a doctoral student at UNC Eshelman School of Pharmacy, University of North Carolina; XL was an employee of GSK during the conduct of the study and holds stock/shares in GSK; RB was a contingency worker, on assignment at GSK at the time of the study and is currently a contingency worker at UCB Biosciences and Lundbeck, Denmark; RS is a former employee of GSK, holds stock/shares in GSK and is a current employee of UCB Biosciences. EB is an employee of GSK and holds stock/shares in GSK.

Authors were in full editorial control of publication target journal, content and conclusions and accepted full responsibility for final approval of a manuscript describing this GSK-sponsored research. As agreed by authors before the preparation of the manuscript began, authors were provided with open and transparent access to data supporting publications including access to data tables, final study reports, case report forms and raw data as needed. The sponsor did not place any restrictions on access to the data or on the statements made in the manuscript.

Author contributions

JD, XL, RB, and RS, contributed to the study concept and design, data acquisition and analysis and interpretation. EB contributed to the study concept and design, and analysis and interpretation.

All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

Funding

The study was funded by GSK (HO-13-13614). This study was approved by CPRD's Independent Scientific Advisory Committee (ISAC), approval number 14_137R.

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