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RESEARCH LETTER

Estimating Inhaled Corticosteroid Exposure from Short-Acting β_2-Agonist–Inhaled Corticosteroid Rescue

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Introduction

Short-acting β_2-agonist (SABA) rescue inhalers provide quick relief of asthma symptoms, but they do not treat underlying airway inflammation. Increasing exposure to SABA alone as rescue therapy is also associated with an increased risk of asthma exacerbations and related emergency department visits and hospitalizations.[1] Moreover, treatment of severe exacerbations with systemic corticosteroids (SCS) can result in a cumulative corticosteroid burden that affects both current and future health.[2] Indeed, cumulative SCS lifetime exposures of ≥500 to 1000 mg compared with >0 to <500 mg are associated with adverse outcomes including type 2 diabetes, anxiety, depression, pneumonia, osteoporosis, and cataracts.[2]

Both the 2023 Global Initiative for Asthma (GINA) report[3] and the US National Asthma Education and Prevention Program (NAEPP) 2020 focused updates to the Asthma Management Guidelines[4] advocate a rescue therapy strategy based on treating symptoms and airway inflammation concomitantly with a fast-acting bronchodilator and inhaled corticosteroid (ICS). The findings of the recent MANDALA study provide support for this approach: as-needed fixed-dose combination albuterol–budesonide 180/160 µg compared with albuterol 180 µg alone demonstrated a 27% reduction in the risk of a severe asthma exacerbation and a 33% reduction in mean annualized total SCS exposure in patients 12 years of age and older with uncontrolled moderate-to-severe asthma receiving a wide range of ICS-containing maintenance therapies and a history of prior-year exacerbations.[5] Of note, overall maintenance adherence remained high during the MANDALA trial (median 84.6%), and the frequency of ICS-associated adverse events was low and comparable in the albuterol–budesonide and albuterol arms.[5]

Data on total ICS exposure from incorporating a SABA-ICS rescue inhaler into real-world practice are currently lacking. The aims of the present study were therefore 1) to use US claims data for adolescents and adults with asthma of all severities to estimate the real-world ICS exposure that would occur from the use of a rescue therapy strategy where each inhalation of SABA was combined with 80 µg of budesonide, and 2) to compare the magnitude of estimated ICS to current observed SCS exposures.

Methods

This descriptive analysis used an observational, retrospective design that assessed 2010–2017 administrative claims from Merative® (formerly IBM®) MarketScan® Research Commercial, Medicaid, and Medicare US databases. In total, 11,972,304 patients with asthma aged ≥4 years with a SABA prescription between 2011 and 2017 were identified. The service date of a random SABA prescription during the study period was defined as the index date. Patients were required to have ≥12 months' continuous medical and pharmacy benefits enrolment before and after the index SABA date (n=5,720,508). To further verify that the analysis was focused on an asthma cohort, patients were required to have

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≥1 inpatient or ≥2 outpatient non-diagnostic claims for asthma during the 12-month pre-index or 60-day post-index time periods, a post-index ICS-based maintenance medication fill totaling ≥32 days' supply and/or ≥1 additional SABA claim, and no evidence of any non-asthma chronic conditions commonly treated with SCS, such as chronic lower respiratory illness other than asthma, primary eosinophilic disorders, cancer, or an autoimmune disorder (n=1,134,143). Patients ≥12 years of age served as the focus of this analysis (n=577,394), with those having observed cumulative ICS or SCS exposures outside the 1st–99.8th percentile of the total cohort removed to ensure the clinical plausibility of the results.

The study used fully anonymized data, and therefore (as per 45 CFR 46.104(d)(4)) institutional review board approval was not necessary. The data source and research activities comply with the procedures set forth in Sections 164.514(a)–(b)1ii of the Health Insurance Portability and Accountability Act of 1996 Privacy Rule. Patients were categorized according to NAEPP treatment steps during the time period of observation using the most common maintenance medication that they filled in the 12-month post-index period. Post-index ICS exposure was assessed based on the proportion of days covered from the observed claims data, and ICS, SABA, and SCS analyses assumed full use of prescription fills. Observed ICS maintenance exposures included all claims for maintenance therapies containing beclomethasone dipropionate, budesonide, ciclesonide, flunisolide, fluticasone furoate, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. These were converted to µg/day fluticasone propionate equivalents based on comparative doses taken from the GINA report and NAEPP guidelines (Table S1).[3,4] Additional ICS exposure that would result from an as-needed fixed-dose combination SABA-ICS of albuterol–budesonide (90 µg albuterol and 80 µg budesonide/inhalation) was projected for the post-index year using mean SABA fills (inhalations/day, based on 200 inhalations/canister multiplied by mean number of post-index canisters). For the total estimated ICS exposure from both maintenance and as-needed use, observed post-index ICS exposure from the claims database was combined with the additional projected ICS exposure, assuming that each inhalation of SABA was combined with 80 µg budesonide (50 µg fluticasone propionate equivalent).[3] Estimated total ICS exposure was compared against maximum acceptable daily ICS ranges, derived for each NAEPP step of ICS therapy from Food and Drug Administration (FDA)-approved fluticasone propionate-based product labels. Annual total estimated ICS exposure was calculated in µg/year fluticasone propionate equivalents by multiplying the estimated total daily ICS exposure by 365 days/year. The estimated total post-index ICS exposure was also compared with the annual mean observed SCS exposure in mg prednisone equivalents among patients with any SCS exposure. Statistics were descriptive and unadjusted. As the study was observational, sample size calculations and powering to show statistical significance were not considered. Mean and standard deviation (mean ±SD) were reported for continuous variables, and percentages for categorical variables.

Results

Of the 577,394 patients with asthma included, 362,861 (62.8%) filled SABA only and 214,533 (37.2%) filled ICS-based maintenance (Figure S1) during the 12-month post-index period. The mean±SD annual number of SABA fills post-index ranged from 2.2±2.2 for the SABA-only group to 4.9±4.8 for the ICS–long-acting β_2-agonist (LABA)–long-acting muscarinic antagonist (LAMA) group, equating to between 1.2±1.2 and 2.7±2.6 SABA inhalations/day, respectively (Table 1).

Figure 1 shows, for each maintenance therapy group, the daily ICS maintenance dose observed (burgundy bars) in the study plus the additional projected as-needed ICS exposure if each SABA inhalation contained 80 µg budesonide (green bars), relative to the maximum FDA-approved daily ICS levels (blue dots). For each maintenance therapy group, the mean observed post-index ICS exposure was below the respective maximum FDA-approved levels, ranging from 24% (high-dose ICS-LABA) to 52% (low-dose ICS) of FDA-approved maximum daily doses. With respect to each therapy level group, if every SABA inhalation was combined with 80 µg budesonide, the projected additional ICS exposure (in fluticasone propionate equivalents) would range from 75 µg/day (low-dose ICS-LABA) to 135 µg/day (ICS-LABA-LAMA). Total estimated ICS exposure from maintenance plus as-needed SABA-ICS would range from 36% (high-dose ICS-LABA) to 100% (low-dose ICS) of respective FDA maximum approved doses.

Of note, a significant proportion of the total patient population (47.5%) received SCS in the post-index year; 51.7% of the SABA-only group and 40.3% of those with maintenance therapy (ranging from 31.5% in the low-dose ICS-LABA group to 56.3% in the ICS-LABA-LAMA group) (Table 1). For all groups receiving maintenance therapies, annual mean±SD post-index SCS exposure for those using any SCS exceeded 500 mg/year prednisone

Table 1 Estimated Total ICS Exposure from Maintenance Plus As-Needed SABA-ICS Relative to Observed SCS Exposure

	SABA Only (n=362,861)	Low-Dose ICS (n=44,385)	Medium/High-Dose ICS (n=35,893)	Low-Dose ICS-LABA (n=23,989)	Medium-Dose ICS-LABA (n=65,081)	High-Dose ICS-LABA (n=43,041)	ICS-LABA-LAMA (n=2144)
Daily exposure							
Observed ICS maintenance dose (µg/day), mean±SD[a]	0	91±56	153±142	79±54	163±120	213±201	271±234
SABA use							
Annual SABA fills							
Mean±SD	2.2±2.2	3.1±2.8	3.6±3.8	2.8±2.7	3.3±3.2	3.9±3.8	4.9±4.8
Median (IQR)	1.0 (0.7, 2.7)	2.0 (1.2, 3.9)	2.0 (1.0, 4.3)	2.0 (1.0, 3.5)	2.0 (1.1, 4.1)	3.0 (1.3, 4.8)	3.0 (1.7, 6.0)
Inhalations/day[b]							
Mean±SD	1.2±1.2	1.7±1.5	2.0±2.1	1.5±1.5	1.8±1.8	2.1±2.1	2.7±2.6
Median (IQR)	0.5 (0.4, 1.5)	1.1 (0.7, 2.2)	1.1 (0.6, 2.4)	1.1 (0.5, 1.8)	1.1 (0.6, 2.2)	1.6 (0.7, 2.6)	1.6 (1.0, 3.3)
Projected additional ICS exposure (µg/day) if each SABA inhalation contained 80 µg BUD[c] (50 µg FP equivalent), mean±SD	60±60	85±75	100±105	75±75	90±90	105±105	135±130
Estimated total ICS exposure from maintenance + as-needed ICS (µg/day), mean	0+60=60	91+85=176	153+100=253	79+75=154	163+90=253	213+105=318	271+135=406
Annual exposure							
Annual total estimated ICS exposure (mg)[a], mean	22	64	92	56	92	116	148
Patients with any SCS exposure, n (%)	187,731 (51.7)	15,298 (34.5)	13,127 (36.6)	7558 (31.5)	27,011 (41.5)	22,327 (51.9)	1206 (56.3)
Annual observed SCS exposure among patients with any SCS exposure (mg), mean±SD[d]	451±1214	555±1138	574±1334	542±1438	590±1365	763±1606	1088±2148
Annual observed SCS relative to estimated ICS exposure	21-fold	9-fold	6-fold	10-fold	6-fold	7-fold	7-fold

Notes: [a]Inhaled corticosteroid dose/day in µg of fluticasone propionate equivalents; [b]calculated by multiplying annual SABA fills by 200 (all SABA canisters approved in the US contain 200 inhalations) then dividing by 365; [c]scaled based on budesonide 80 µg equating to 50 µg fluticasone propionate, as per GINA 2021; [d]cumulative annual systemic corticosteroid exposure in mg of prednisone equivalents.

Abbreviations: BUD, budesonide; FP, fluticasone propionate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist; SCS, systemic corticosteroid; SD, standard deviation.

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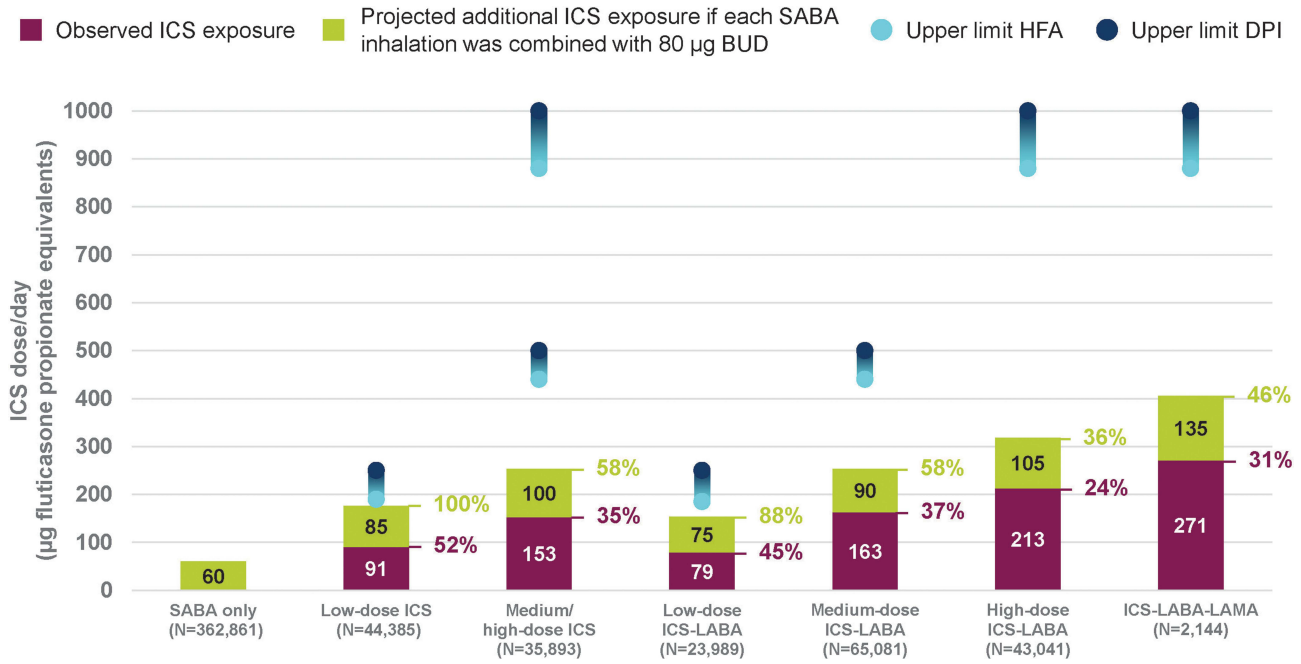

Figure 1 Observed ICS exposure and projected additional as-needed ICS exposure if each SABA inhalation contained 80 µg budesonide, relative to maximum FDA-approved doses, by maintenance group.

Notes: Percentage values in burgundy indicate the percentage of FDA-approved maximum daily ICS dose reached with observed ICS maintenance therapy; percentage values in green indicate the percentage of FDA-approved maximum daily ICS dose reached with observed ICS maintenance therapy plus projected additional as-needed ICS exposure if each SABA inhalation contained 80 µg budesonide. Data can also be seen in Table 1.

Abbreviations: BUD, budesonide; DPI, dry powder inhaler; FDA, Food and Drug Administration; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-actingβ_2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist.

equivalents (the threshold level vs >0 to <500 mg that is associated with an increased risk of chronic adverse health conditions[2]) and ranged from 542±1438 mg in the low-dose ICS-LABA group to 1088±2148 mg in the ICS-LABA-LAMA group (Table 1). For those patients with post-index SCS exposure in the SABA-only therapy group, annual mean±SD post-index exposure was 451±1214 mg/year. For comparison, in the MANDALA study, the mean±SD annualized total dose of SCS (in prednisone equivalents) was 83.6±247.7 mg in the higher-dose combination group and 130.0±630.3 mg in the albuterol alone group. Total annual mean estimated ICS exposure (mg of fluticasone propionate equivalents, including observed ICS claims and projected additional as-needed ICS) ranged from 22 mg in the SABA-only group to 148 mg in the ICS-LABA-LAMA group. Among patients receiving any post-index SCS, annual estimated total mean mg of ICS exposure were 6–21-fold lower (medium/high-dose ICS and SABA-only groups, respectively) than observed annual post-index mean mg of SCS exposure.

Discussion

This medical and pharmacy claims study of over half a million US adolescent and adult patients with asthma of all disease severities shows that the estimated mean total annual ICS exposure from use of a SABA-ICS rescue would remain within the range of FDA-approved ICS dosing at each step of therapy, if as-needed SABA-ICS continued at the same level as current SABA use. These estimations should serve to assuage concerns at a real-world population level regarding the risk of excessive ICS exposure from the budesonide component of an albuterol–budesonide fixed-dose combination rescue therapy. Our observations also highlight that under the decades-old asthma rescue and maintenance therapy paradigm that employs as-needed SABA without concomitant ICS, many patients are poorly adherent to maintenance medication and experience annual SCS exposures of ≥500 to 1000 mg, a lifetime threshold associated with adverse chronic health conditions.[2]

Our finding that total annual estimated mean ICS exposure was several-fold lower than the mean annual observed SCS exposure that occurred in the almost 50% of the population who had post-index SCS use, represents a large potential

opportunity to reduce SCS exposure and associated adverse health outcomes if as-needed SABA is replaced with SABA-ICS. Use of albuterol with concomitant ICS as rescue therapy has been shown to significantly decrease exacerbations and SCS exposure in patients with moderate-to-severe asthma.[5,6] Notably, the 27% reduction in risk of severe exacerbations and 33% decrease in annualized SCS exposure reported in MANDALA are potentially underestimations relative to potential real-world outcomes, given the much higher adherence to maintenance medications reported in MANDALA compared with the current analysis of real-world data for each of the therapy groups.

When comparing mg of estimated ICS to mg of observed SCS exposure, it is important to note that ICS formulations exert their anti-inflammatory activity locally in the airways, which lessens their potential to cause systemic adverse effects. In comparison to the oral corticosteroid prednisolone, the molecular structural features of ICS result in greater corticosteroid receptor binding affinity and selectivity, lipophilicity, and plasma protein binding, and lower aqueous solubility.[7] These pharmacologic features of ICS relative to oral corticosteroids serve to drive topical anti-inflammatory activity and enhanced targeting to the airways, while reducing systemic exposure.[7]

The strength of our study is that the analysis is based on real-world claims data and includes a large number of patients with a range of healthcare insurance types across the full spectrum of asthma severities, exacerbation histories, and levels of asthma control. Limitations include those inherent to all studies of claims data: results may not be generalizable to all patients with asthma (although the current study's sample size and diversity of patients' asthma status are mitigating factors for this limitation), and measures of medication utilization were based on filled prescriptions and may not reflect actual patient usage. In fact, a strong assumption of our analysis is that all SABA inhalations for the fills observed were used, although in reality this is unlikely; thus, our calculations of as-needed ICS exposure may well overstate the projected additional ICS exposure that would occur with the use of a fixed-dose combination rescue therapy. The focus of this analysis was purely on ICS and SCS exposures at a population level; we did not have the ability to assess individual patient data, and therefore variance for estimated mean total ICS exposure was not available and outliers in each therapy group with ICS exposures above FDA recommendations could not be identified. However, given the wide margin for the high-dose ICS groups observed in the current analysis, as well as the potential for SCS reduction and the safety data from the MANDALA clinical trial, most patients using high-dose ICS would not be expected to receive excessive corticosteroid exposure from an asthma management regimen utilizing as-needed SABA-ICS.

Conclusions

Our study estimations show that ICS exposure from a SABA-ICS rescue therapy would remain within the range of FDA-approved doses, and that patients with asthma of all disease severities and maintenance treatments could benefit from reduced exposure to SCS with a fixed-dose combination SABA-ICS versus albuterol alone as rescue.

Abbreviations

BUD, budesonide; DPI, dry powder inhaler; FDA, Food and Drug Administration; GINA, Global Initiative for Asthma; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NAEPP, National Asthma Education and Prevention Program; SABA, short-acting β_2-agonist; SCS, systemic corticosteroid.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy, described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org.

Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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IG, MP, and HG are employees of, and own stock in, AstraZeneca.

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