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SHORT REPORT

Patterns of Rescue and Maintenance Medication Claims Surrounding an Asthma Exacerbation in Patients Treated as Intermittent or Mild Persistent Asthma

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Purpose: To examine patterns of short-acting ß$_2$-agonist (SABA) and maintenance therapy claims surrounding the subset of severe asthma exacerbations associated with outpatient, urgent care, or emergency department visits or hospitalization (termed serious exacerbations) in patients treated as intermittent or mild persistent asthma.

Methods: This was a retrospective study of 2010–2017 administrative claims from Merative™ MarketScan® US databases for patients ≥12 years filling a SABA prescription for asthma (index). Patients had ≥12 months continuous insurance eligibility pre- and post-index and ≥1 additional SABA and/or maintenance medication fill appropriate for mild persistent asthma post-index. Prescription fills were assessed over 30 days before and after a serious exacerbation event.

Results: Of 323,443 patients (mean [standard deviation] age: 34.9 [18.2] years; 62.0% female) treated as intermittent or mild persistent asthma, 51,690 (16.0%) experienced ≥1 serious exacerbation post-index. During the 30 days pre-event, a greater proportion of patients filled a SABA versus maintenance therapy (24.6% vs 19.0%; odds ratio [OR]: 1.39, 95% confidence interval [CI]: 1.35–1.43; $p < 0.001$); during the 30 days post-event, patients were more likely to fill maintenance medication versus SABA (88.6% vs 67.0%; OR [95% CI]: 3.88 [3.75–4.01]; $p < 0.001$). The closer in time prior to the event, the greater the likelihood of filling a SABA versus maintenance prescription (OR [95% CI]; 1–7 days pre-event: 1.42 [1.36–1.48]; 8–14 days pre-event: 1.34 [1.27–1.41]; 15–30 days pre-event: 1.18 [1.12–1.24]; all $p < 0.001$). Over 4.5 times more patients filled a maintenance therapy within 7 days post-event (45,014) versus all 30 days pre-event (9835) (OR [95% CI]: 28.7 [27.7–29.7]; $p < 0.001$).

Conclusion: These patterns of SABA rescue and maintenance fills suggest that a "window of opportunity" may exist to interrupt a serious exacerbation occurrence for patients treated as intermittent or mild persistent asthma if symptoms and inflammation are addressed concomitantly.

Keywords: asthma, corticosteroid, inflammation, maintenance therapy, rescue therapy, short-acting ß$_2$-agonist

Introduction

Asthma exacerbations remain a major health burden in the United States (US), and even patients with intermittent or mild persistent asthma are at risk of experiencing severe exacerbations.[1] Approximately 60% of US patients treated as intermittent asthma experience a severe exacerbation in a given year, and 30–40% of asthma-related emergency department (ED) admissions occur in patients treated as mild asthma.[2,3]

Airway inflammation is central to asthma symptoms and exacerbations. In the days leading up to an exacerbation, lung function decreases and symptoms and use of short-acting ß$_2$-agonist (SABA) rescue therapy increase.[4] Although

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SABA alone relieves symptoms, it does not treat the accompanying increase in airway inflammation, leaving patients at risk of exacerbations.[1] A window of opportunity may exist to prevent exacerbations if symptoms and inflammation are treated concomitantly. Indeed, the latest recommendations from the Global Initiative for Asthma (GINA), US National Asthma Education and Prevention Program (NAEPP), and European Respiratory Society support fast-acting bronchodilator/inhaled corticosteroid (ICS) rescue for some, if not all, patients aged ≥12 years with asthma.[1,5,6]

To further visualize this window of opportunity in the real-world setting and understand patient behaviors during the vulnerable period leading up to exacerbations, we previously analyzed medical and pharmacy administrative claims of US patients filling prescriptions appropriate for moderate-to-severe persistent disease before and after an exacerbation associated with an outpatient, urgent care, or ED visit or a hospitalization for asthma. These analyses revealed that many patients treated as moderate-to-severe asthma escalated SABA claims in the 30 days prior to an exacerbation event, yet approximately 40% had no maintenance therapy fills during this period, potentially leaving them unprotected from increasing airway inflammation.[7] The objective of the current analyses was to extend these evaluations to patients treated as intermittent or mild persistent asthma, exploring whether in this presumably less severe population, patterns of medication use also suggest a window of opportunity to prevent exacerbations.

Methods

This was an observational, retrospective study of 2010–2017 administrative claims from US Merative™ MarketScan® Research Databases. Patients aged ≥12 years filling a SABA prescription for asthma between January 1, 2011, through December 31, 2016, were identified. The date of a random SABA claim during the study period was defined as the index date. Patients were required to have ≥1 inpatient or ≥2 outpatient non-diagnostic claims for asthma during the 12-months pre-index or within 60-days post-index, ≥12 months' continuous medical and pharmacy benefits pre- and post-index, and ≥1 additional SABA and/or maintenance medication fill appropriate for mild persistent asthma post-index. Patients with chronic conditions other than asthma commonly treated with systemic corticosteroids (SCS) were excluded. Patients with post-index maintenance fills totaling <32 days' supply were classified as being treated as intermittent asthma (SABA only: GINA(2018)/NAEPP(2007) Step 1 classifications). Fully anonymized data were analyzed; therefore, as per 45 CFR 46.104(d)(4), institutional review board approval was not required. 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.

Severe asthma exacerbations were identified from medical and pharmacy claims during the 12-month post-index period and were defined as follows: 1) prescription fills for SCS treatment with ≥3 days' supply of oral corticosteroids or a single corticosteroid injection for patients without chronic SCS, or any overlap of two SCS medications of >7 days' supply (either oral or injection) for patients with chronic use of SCS; 2) an ED or other outpatient visit with a primary diagnosis of asthma exacerbation and receiving SCS within a 5-day window from the date of the visit; or 3) an inpatient admission with a primary diagnosis of asthma. Serious exacerbations were those subsets of severe exacerbations accompanied by an in-person healthcare clinician encounter in an outpatient clinic, urgent care, or ED, or hospital admission. SABA and maintenance fills were assessed in the 30-day period before and after a serious exacerbation event.

Analysis of 30-day pre- and post-exacerbation patterns of SABA and maintenance therapy fills included only serious exacerbations and were compared using unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) calculated using MedCalc Statistical Software (Ostend, Belgium; https://www.medcalc.org); significance was $p \leq 0.05$.

Results

A total of 323,443 patients ≥12 years of age treated as having intermittent or mild persistent asthma were identified. The mean (standard deviation [SD]) age was 34.9 (18.2) years, and 62.0% were female. Most patients had commercial insurance (70.4%) and the remainder either Medicaid (24.9%) or Medicare (4.7%). Among these patients, 215,363 (66.6%) filled SABA only or SABA with <32 days of maintenance therapy appropriate for mild persistent asthma; whereas 80,162 (24.8%) filled leukotriene modifiers, 27,833 (8.6%) filled low-dose ICS, and 462 (0.1%) filled methylxanthines with ≥32 days' supply along with SABA.

In the 12-month post-index period, patients had a mean (SD) of 2.7 (2.7) SABA fills, with 41.4% of patients having 1 fill, 26.2% 2 fills, 12.9% 3 fills, and 19.5% ≥4 SABA fills. Post-index, 199,718 (61.7%) patients experienced a severe exacerbation. Serious exacerbations were experienced by 51,690 (16.0%) patients; of these, 86.9% had 1 event, 10.6% 2 events, 1.9% 3 events, and 0.7% ≥4 events (mean [SD] of 1.2 [0.5] events/person).

In the 30 days prior to a serious exacerbation, approximately 1 in 4 patients filled a SABA (24.6%; n = 12,704) and 1 in 5 filled a maintenance medication prescription (19.0%; n = 9835) (Figure 1). In the 30 days following a serious exacerbation, roughly 2 out of every 3 patients (67.0%; n = 34,635) filled a SABA and 4 out of 5 (88.6%; n = 45,823) filled a maintenance therapy. Although the likelihood of filling a SABA versus a maintenance therapy was significantly greater in the 30 days prior to a serious exacerbation (OR 1.39 [95% CI 1.35–1.43]; p < 0.001), in the 30 days after the event, patients were more likely to fill a maintenance medication versus a SABA (OR 3.88 [95% CI 3.75–4.01]; p < 0.001).

For those patients who experienced a serious exacerbation, the closer in time prior to the event, the greater the number filling a SABA versus a maintenance prescription (Figure 2A). In the 1–7 days pre-exacerbation, 5716 patients filled a SABA versus 4156 a maintenance medication (OR 1.42 [95% CI 1.36–1.48]; p < 0.001); 8–14 days pre-exacerbation: 3138 versus 2385 (OR 1.34 [95% CI 1.27–1.41]; p < 0.001); 15–30 days pre-exacerbation: 3850 versus 3294 (OR 1.18 [95% CI 1.12–1.24]; p < 0.001). Over 4.5 times more patients filled a maintenance therapy in the 7 days after a serious exacerbation event (45,014) than in the entire 30 days before (9835) (OR 28.7 [95% CI 27.7–29.7]; p < 0.001). For comparable time periods, the closer to the serious exacerbation, the greater the odds of patients filling a maintenance therapy following versus before the event (Figure 2B); 1–7 days following versus 1–7 days before: OR 77.1 (95% CI 74.0–80.3); 8–14 days following versus 8–14 days before: OR 49.4 (95% CI 47.6–51.3); 15–30 days following versus 15–30 before: OR 33.2 (95% CI 32.1–34.3); p < 0.001 for each time-period comparison.

Discussion

This study of medical and pharmacy claims data from US patients ≥12 years of age treated as intermittent or mild persistent asthma revealed patterns of SABA and maintenance medication fills prior to and following a serious exacerbation. In the 30 days before, SABA fills were progressively greater than those for maintenance medication, with 81% of patients not filling anti-inflammatory therapy. Almost all patients went on to fill a maintenance therapy in the 30 days following a serious exacerbation. These prescription fill patterns imply that during the time period leading up to an

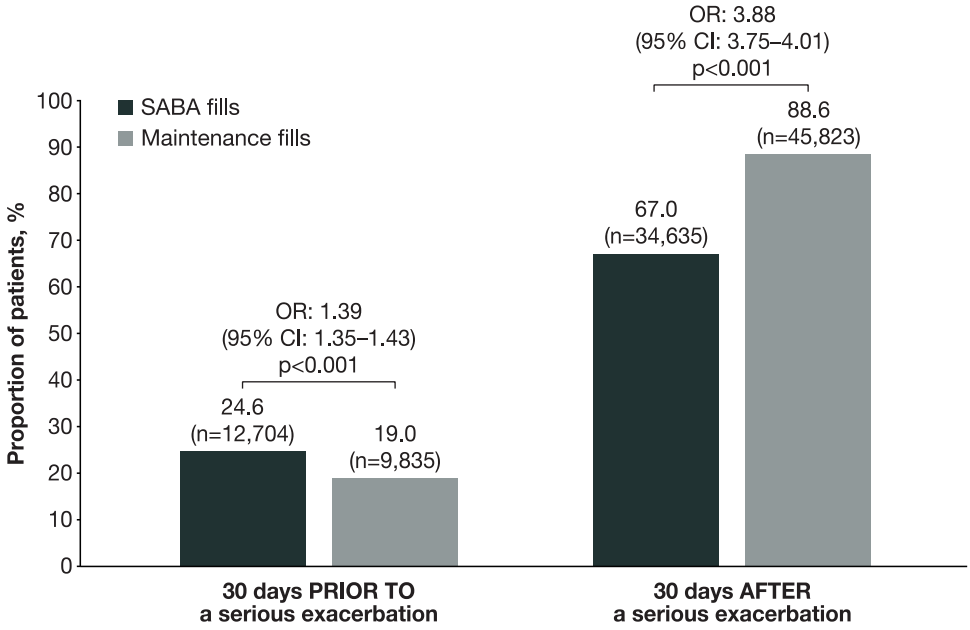

Figure 1 Proportion of patients filling SABA and the proportion filling mild persistent maintenance therapy prior to and after a serious exacerbation (N=51,690). Prior to a serious exacerbation: odds of filling a SABA versus a maintenance medication; after a serious exacerbation: odds of filling a maintenance medication versus a SABA.
Abbreviations: CI, confidence interval; OR, odds ratio; SABA, short-acting β_2-agonist.

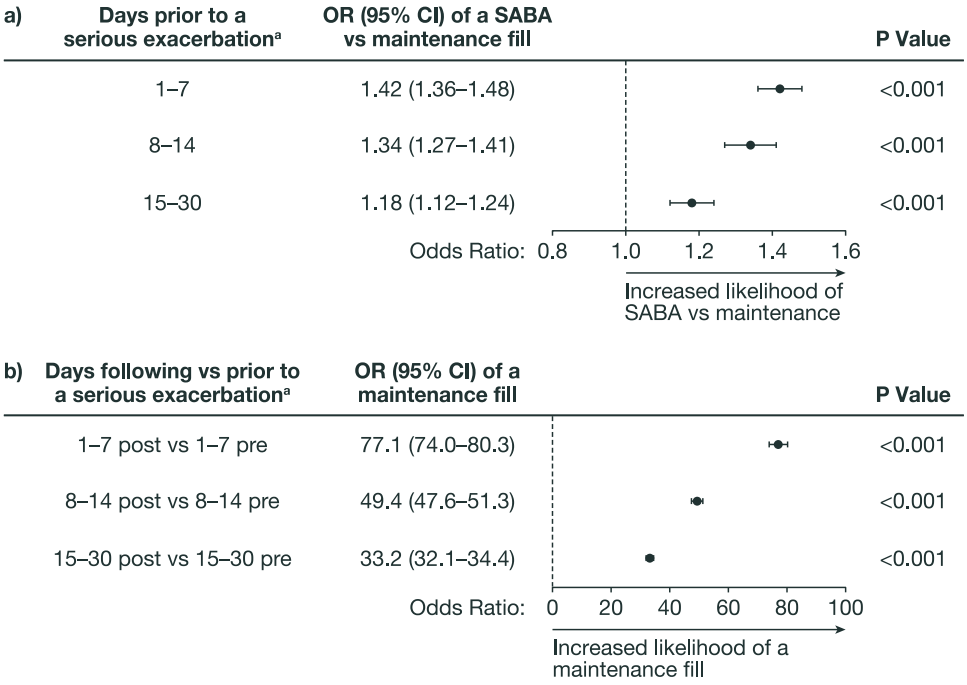

Figure 2 (**a**) Odds of filling a SABA versus a maintenance therapy prescription appropriate for mild persistent asthma before a serious exacerbation; (**b**) Odds of filling a maintenance therapy prescription appropriate for mild persistent asthma over comparable time periods following versus prior to a serious exacerbation.
Notes: [a]1–7 days prior to refers to the time period from 1 day before up to 7 days before a serious exacerbation; 8–14 days prior to refers to the time period from 8 days before up to 14 days before a serious exacerbation; 15–30 days prior to refers to the time period from 15 days before up to 30 days before a serious exacerbation.
Abbreviations: CI, confidence interval; OR, odds ratio; SABA, short-acting β_2-agonist.

exacerbation, many patients either have not been prescribed and/or do not have anti-inflammatory maintenance medication on hand. After an exacerbation event, these patients and/or their clinicians may have recognized the need to fill for anti-inflammatory therapies. However, this reactive approach to escalating anti-inflammatory therapy did not prevent 13.1% of those patients from having subsequent asthma exacerbation-related hospitalizations or outpatient clinic, urgent care, or ED visits.

These observed patterns of rescue and maintenance fills reflect known patient behavior to downplay the need for daily maintenance medication and prioritize quick symptom relief when needed, as demonstrated in the INSPIRE study.[8] However, these patterns may also indicate that patients had not been considered for maintenance medication until the occurrence of a serious exacerbation. This approach to the types of therapies that are utilized by patients treated as having intermittent and mild persistent asthma represents a missed window of opportunity to interrupt the rising inflammation that precedes an exacerbation if SABA and ICS were used concomitantly for symptom treatment.

Our observations support the GINA construct that SABA-only treatment of asthma (without concomitant ICS) can no longer be recommended.[1] GINA recommends ICS plus the fast-acting bronchodilator formoterol as the preferred rescue option across all treatment steps in Track 1 for patients ≥12 years.[1] Concomitant use of as-needed SABA and ICS is included as a GINA Track 2 rescue option when Track 1 is not possible and as a NAEPP preferred treatment option for patients ≥12 years with mild persistent asthma.[1,5] On a cautionary note, GINA states that before prescribing a regimen with SABA as rescue, consider whether the patient is likely to be adherent with their maintenance therapy, as if not, they will be at higher risk of exacerbations. Barriers to the as-needed use of ICS-formoterol exist in the US, as this therapy is not FDA-approved for rescue or maintenance-and-rescue therapy. A fixed-dose combination albuterol-budesonide pressurized metered-dose inhaler has been approved (January 2023) by the FDA for as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma of all disease severities aged ≥18 years.[9] This approval was supported by the Phase 3 MANDALA study, in which as-needed albuterol-budesonide 180/160 µg significantly reduced the risk of a severe exacerbation by 28% compared with as-needed albuterol in symptomatic patients ≥18 years treated for moderate-to-severe asthma with ICS-containing maintenance therapy.[9,10] Ongoing trials are evaluating exacerbation reduction with albuterol-budesonide in patients treated as intermittent and mild persistent asthma.

Our findings on patterns of SABA and maintenance fills surrounding a serious exacerbation in patients treated for intermittent and mild persistent asthma are broadly consistent with those we reported previously in patients with moderate-to-severe asthma from the same US claims database.[7] These previous data also highlighted a reactive approach to filling maintenance prescriptions post-serious exacerbation, with many patients potentially being unprotected against increasing airway inflammation prior to an exacerbation. Similar to the current study, patients treated as having moderate-to-severe asthma had increasing SABA claims prior to a serious exacerbation, with 43% not filling their maintenance medication in the 30 days before the exacerbation event.[7] In the 30 days post-exacerbation, 95% filled a maintenance medication.[7] Similar to the current analyses, despite this post-exacerbation increase in maintenance medication fills, over 27% of these patients experienced additional serious exacerbations.[7]

It is noteworthy that the morbidity of the population studied in the current analyses was high, with almost two-thirds having ≥1 severe exacerbation resulting in systemic steroid exposure in the post-index year and one-third filling ≥3 SABA canisters annually. Moreover, two-thirds were treated as having intermittent asthma. These findings highlight the need to reconsider the concept of whether any patient with asthma should be classified as having intermittent disease. The GINA report[1] states that Guidelines such as those of the NAEPP,[5] which include disease severity classifications that distinguish between intermittent and mild persistent asthma, have used arbitrary criteria of SABA utilization to determine which patients were not at risk or would not benefit from ICS treatments and could be managed with SABA alone. However, as stated in GINA and shown in the current analyses, patients treated as intermittent asthma can have severe exacerbations.[1]

In the current study, the magnitude of the unmet need for intermittent asthma is underscored by over two-thirds of all mild asthma patients relying on rescue bronchodilators alone, with the intermittent group having the highest proportion of patients experiencing exacerbations. Our results draw attention to a critical omission in the latest NAEPP update,[5] in which the treatment recommendation for intermittent asthma is SABA-only, a concept at odds with the GINA's Step 1 preferred regimen of as-needed low-dose ICS-formoterol.

Limitations of the current study are those associated with analyses of prescription claims data. Measures of medication utilization were based on filled prescriptions and may not reflect actual or technically adequate use. Although it is possible patients may have taken SCS for other reasons, these patients had asthma and exacerbations. Descriptions of asthma severity were indicative only, as they were based on filled prescriptions only; other criteria of severity could not be assessed. Patients were assumed to have taken the medication prescriptions that they filled, but this cannot be confirmed with claims data. We are unable to assess underlying indices of asthma pathophysiology relative to lung function or inflammation and cannot ascertain frequencies of specific symptom impairments to confirm disease severity or control. The data are purely observational and not adjusted for any potential confounding variables. Although these patients filled therapies appropriate for intermittent and mild persistent disease, they may have been assessed by their clinicians as having moderate to severe asthma but did not fill prescribed therapies for these severity levels. Results of this analysis may not be generalizable to patients with insurance types not contained within the Merative™ MarketScan® Research Databases or without any healthcare coverage. Although a patient may not have filled a SABA or maintenance prescription in the 30 days prior to a serious exacerbation, they may have had previously filled but unused medication remaining on hand.

Conclusions

The patterns of SABA rescue and maintenance prescription fills revealed in this study suggest that a window of opportunity may exist to interrupt the occurrence of serious exacerbations in adolescents and adults treated for intermittent or mild persistent asthma if a fast-acting bronchodilator and an ICS are used concomitantly for rescue, as opposed to SABA alone.

Abbreviations

CI, confidence interval; ED, emergency department; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; NAEPP, National Asthma Education and Prevention Program; OR, odds ratio; SABA, short-acting ß2-agonist; SCS, systemic corticosteroid; SD, standard deviation; US, United States.

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 could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. 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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AstraZeneca funded the study and had a role in the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data and had final responsibility to submit for publication.

Disclosure

MJL has been a speaker for Amgen/AstraZeneca, Sanofi/Regeneron; consultant for Amgen, AstraZeneca, Cogent, Genentech, Grifols, Novartis, Sanofi, Regeneron; and has received research support from AstraZeneca, Genentech/Roche, Sanofi/Regeneron. MP and IAG are employees and stock owners of AstraZeneca. HNG was an employee and stock owner of AstraZeneca at the time of the study and is now an employee of Alexion, AstraZeneca Rare Disease Unit. JPT was an employee of IBM Watson Health at the time of the study, which received funding from AstraZeneca to conduct this study. He is now an employee of Health Economics and Outcomes Research, Inovalon, Washington, DC. NLL has received research funding from Amgen, Avillion, Janssen, Sanofi, GSK, Genentech, TEVA, Regeneron, and AstraZeneca and consulting fees from AstraZeneca, GSK, and Teva; served on advisory boards for Sanofi, Astra Zeneca, Genentech, TEVA, Amgen, and GSK; and received honoraria for non-speaker bureau presentations from AstraZeneca and GSK.

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