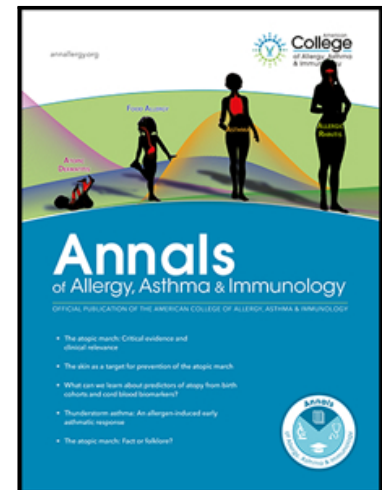


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A real-world study of ICS use in patients with severe eosinophilic asthma treated with mepolizumab

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Abbreviations/Acronyms: ED, emergency department; FP, fluticasone propionate; GINA, Global Initiative for Asthma; HCP, healthcare practitioner; ICD, International Classification of Diseases; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MCS, mast cell stabilizers; OCS, oral corticosteroids; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SEA, severe eosinophilic asthma; SD, standard deviation

Background: Mepolizumab is a humanized anti-interleukin-5 monoclonal antibody approved for the treatment of patients with severe eosinophilic asthma (SEA). There is limited evidence that patients treated with mepolizumab can reduce inhaled corticosteroid (ICS) use.

Objective: To investigate changes in ICS use and clinical outcomes in patients with SEA who initiated mepolizumab treatment.

Methods: This retrospective cohort study (GSK ID: 212695/HO-20-19951) used administrative claims data from the IBM Watson Health MarketScan Database (identification period: November 2015–March 2018). Eligible patients had SEA and were receiving high-dose ICS and mepolizumab. ICS, oral corticosteroid (OCS), short acting β 2-agonist (SABA) use, and exacerbation frequency were analyzed quarterly during the 12-month follow-up period following mepolizumab initiation.

Results: In total, 351 patients were included. The proportion of patients using highdose ICS decreased in quarters 1–4 following mepolizumab initiation (79.8%, 74.6%, 68.9%, 65.5%, respectively); 49.0% of patients reduced or discontinued ICS for ≥ 1 quarter. Comparing patients who discontinued ICS versus those who remained on high-dose ICS, a lower proportion had chronic OCS use (3.4–9.2% vs 13.9–16.8%) and OCS burst use (15.4–20.8% vs 19.7–26.1%) in quarters 1–4; similarly in quarters 3 and 4, a lower proportion of patients had exacerbations (16.9% and 20.3% vs 27.2% and 27.7%) and SABA claims (35.4% and 39.2% vs 43.3% and 49.0%, respectively). **Conclusion:** In patients with SEA on high-dose ICS, a reduction in both ICS and OCS use was observed after initiating mepolizumab. These findings have important implications for clinical outcomes and follow-up care in this patient population.

Introduction

Patients with severe asthma may require chronic treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or oral corticosteroids (OCS).¹ While emphasis is often placed on the adverse effects and importance of reduction of OCS, prolonged ICS use also has the potential for significant local and systemic side effects.^{2–4} The systemic effects of prolonged ICS use increase with dosage, with many ICS demonstrating an increased systemic activity to therapeutic ratio at high doses (≥ 500 μ g/day fluticasone propionate [FP]-equivalent as defined by the Global Initiative for Asthma [GINA]

statement¹¹) than at low or medium doses.^{2, 5} Thus, prolonged high-dose ICS has been associated with many of the same serious adverse effects as OCS use in patients with asthma, including a 2.5-fold increased risk of suppression of the hypothalamic–pituitary–adrenal axis, 0.5 cm/year reduced growth velocity in children, and a 63% and 30% increased risk of osteoporosis and diabetes, respectively.⁶⁻¹⁰ Reflecting the potential adverse effects of corticosteroids, the European Respiratory Society-American Thoracic Society guidelines and GINA statement on asthma management both recommend the stepwise reduction of first OCS followed by ICS dosage whenever possible.^{1, 11} This also highlights the need for add-on treatments, which allow for a reduction in OCS use while maintaining disease control. Identifying whether add-on treatments may also result in changes in ICS dosage may offer an additional opportunity to reduce corticosteroid exposure.

Mepolizumab, a humanized anti–interleukin-5 monoclonal antibody is an add-on maintenance treatment approved for severe eosinophilic asthma.¹² Mepolizumab has demonstrated consistent and sustained efficacy in reducing asthma exacerbations and OCS use, as well as improving symptoms, health-related quality of life and lung function in placebo-controlled and open-label extension trials.¹³⁻¹⁸ The efficacy of mepolizumab has also been demonstrated in real-world studies.¹⁹⁻²² Previous real-world studies have suggested that mepolizumab use is associated with a reduction in the proportion of patients receiving ICS.²⁰ Whilst a recent real-world study investigated patterns of ICS adherence after mepolizumab initiation, changes to prescribed ICS dosage were not assessed.²³ To the best of our knowledge, changes in ICS dosage following mepolizumab initiation have not previously been formally investigated in a real-world study.

The objective of this study was to investigate changes in ICS use in patients receiving high-dose ICS, who initiated mepolizumab treatment for severe eosinophilic asthma. In addition,

we sought to determine whether changes in ICS use were associated with changes in important clinical outcomes, including asthma exacerbations, OCS use, and short-acting β_2 -agonist (SABA) use.

Methods

Data source and study design

This was a retrospective cohort study of patients with asthma who received mepolizumab, using administrative claims data from the IBM Watson Health MarketScan Commercial Claims and Encounters Database and the MarketScan Medicare Supplemental Database. The MarketScan Commercial Database contains the inpatient, outpatient, and outpatient prescription drug experience of employees and their dependents, covered under a variety of fee-for-service and managed care health plans, including exclusive provider organizations, preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations. The MarketScan Medicare Supplemental Database contains the healthcare experience (both medical and pharmacy) of retirees with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as a Coordination of Benefits Amount) and the employer-paid portion are included in this database. Both the MarketScan Commercial and Medicare Databases provide detailed costs, prescription drug use, and outcomes data for healthcare services performed in both inpatient and outpatient settings, covering approximately 147.9 million lives. The medical claims are linked to outpatient prescription drug claims and person-level enrollment data using unique enrollee identifiers.

Patients with asthma were identified who had a medical or pharmacy claim for mepolizumab administration between November 1, 2015 and March 31, 2018 (identification period), with the index date designated as the date of the first claim for mepolizumab administration. Data

were gathered for the 12 months prior to the index date (the baseline period) and the 12 months following the index date (the follow-up period). A post hoc analysis gathered data for a subset of patients with 24 months of continuous enrollment following the index date (24-month follow-up period; **eFigure 1**).

No direct patient contact or primary collection of individual human patient data occurred. Study results are in tabular form and presented as aggregate analyses that omit patient identification, therefore informed consent, ethics committee or IRB approval was not required.

Patient population

Eligible patients were ≥ 12 years of age with ≥ 1 diagnosis of asthma in any position on a nondiagnostic medical claim during the baseline period, a medical or pharmacy claim including mepolizumab during the identification period and evidence of ≥ 2 mepolizumab administrations during the first 180 days of the follow-up period. Patients were also required to have evidence of high-dose ICS use (as defined by the GINA 2018 statement; **Table 1**)²⁴ in the last 90 days of the baseline period and 12 months' continuous enrollment with medical and pharmacy benefits before and after the index date. Patients with evidence of mepolizumab use during the 12-month baseline period or evidence of omalizumab, reslizumab, benralizumab, or dupilumab use during the baseline or follow-up period were excluded. Diagnostic and medication claims codes used in patient identification are given in **eTable 1**.

Outcomes and assessments

All primary and secondary outcomes were measured per quarter during the 12-month follow-up period. Quarterly intervals were selected in order to capture changes in outcome measures over time relative to the last 90 days (quarter) of the baseline period that was used to establish

high-dose ICS use. The primary outcome measure was ICS use in each quarter of the 12-month follow up period. ICS dose was determined using the most recent ICS/long-acting β_2 -agonist (LABA) combination pharmacy claim within each quarter and classified as low, medium, or high as defined in **Table 1**. Patients without any ICS/LABA claims were assigned to minimal-, low-, medium-, or high-dose category (defined in **Table 1**), according to the highest dose of the ICS single agent claims in the quarter. Definitions of ICS dose were as defined by the GINA statement 2018.²⁴

The secondary outcomes were the proportion of patients with chronic OCS use, ≥ 1 OCS burst, ≥ 1 asthma exacerbation, and ≥ 1 SABA claim during each quarter of the follow-up period, each stratified by ICS use category (high, other, none). Asthma exacerbations were defined as an outpatient or emergency department (ED) claim with a diagnosis of asthma and ≥ 1 claim for OCS in the prior 4 or following 5 days, or an inpatient admission with a diagnosis of asthma as the primary diagnosis. In line with a previous study²², chronic OCS use was defined as a mean daily OCS dose of ≥ 10 mg prednisone equivalent throughout a given 3-month quarter, calculated using days' supply, strength, and metric quantity on pharmacy claims. OCS bursts were defined as an average daily dose of ≥ 20 mg prednisone equivalent for 3–28 days and an outpatient or ED claim with a diagnosis of asthma in any position on a nondiagnostic medical claim in the prior 7 or following 6 days. Among patients who discontinued ICS, exacerbations, OCS use, and SABA use were also assessed in the quarter prior to discontinuation.

Patient demographic and clinical characteristics were assessed at index or during the baseline period. Comorbid conditions were identified by International Classification of Diseases (ICD)-9/ICD-10 diagnosis codes on medical claims. The use of asthma medications (ICS, SABA, short-acting muscarinic antagonists, LABA, long-acting muscarinic antagonist,

leukotriene receptor antagonist [LTRA], and mast cell stabilizers during the baseline and follow-up periods were also assessed. A post hoc analysis was carried out in patients with ≥ 24 months enrollment after the index date, which assessed ICS use during each quarter of the 24-month follow-up period in patients stratified by ICS discontinuation category (discontinued ICS at any time during follow-up or did not discontinue ICS during follow-up).

Statistical analysis

For all patient demographics, baseline clinical characteristics, and primary and secondary outcomes, the mean and standard deviation (SD) were reported for continuous variables, and the counts and percentages were reported for the nominal or categorical variables. Sankey plots were generated to examine quarterly changes in ICS use. As part of the 24-month post hoc analyses, statistical comparisons of outcomes between patient populations discontinuing ICS at any point during the 24-month follow-up versus those who did not discontinue were conducted. Continuous variables and categorical variables were compared using *t*-tests and chi-squared tests, respectively.

Results

Patient population

In total, 351 patients met the eligibility criteria and were included in the study. Patient baseline characteristics are described in **Table 2**; most patients were female (62.0%), with a mean age of 52.1 years. Overall, a high proportion of patients had comorbidities, including respiratory conditions; 71.5% of patients had allergic rhinitis, 57.0% had sinusitis (42.7% chronic sinusitis), and 31.3% had COPD. Respiratory-related symptoms and procedures were also common; 93.2% of patients had a pulmonary function test during baseline while 63.2% had a chest X-ray (**Table 2**).

Use of mepolizumab and other asthma therapies

The mean (SD) number of mepolizumab injections/claims per patient during the 12-month follow-up period was 10.7 (4.2), with a mean (SD) of 35.8 (16.8) days between injections/claims. With regard to adherence, 233 (66.4%) patients had ≥ 10 mepolizumab claims during the 12-month follow-up period and 58 (16.5%) patients had a gap > 12 weeks between claims.

The most commonly used asthma medications during the baseline period were ICS/LABA combination drugs (94.9%), followed by SABA (84.0%) and LTRA (78.6%). The proportion of patients using all non-mepolizumab asthma medications during the 12-month follow up period was lower than during the baseline period, with the exception of mast cell stabilizers (Cromolyn Sodium and Nedocromil Sodium), for which use was the same in both periods (**Figure 1**).

ICS use and other outcomes during the 12-month follow-up period

ICS (excluding ICS/LABA) was used by 47.6% of patients during the baseline period and 35.0% of patients during the 12-month follow-up period. Overall, 14 (4.0%) patients completely discontinued ICS use for the duration of the 12-month follow-up period.

Approximately half of patients (172; 49.0%) were able to discontinue or reduce ICS for at least 1 quarter and 125 (35.6%) patients were able to discontinue ICS for at least 1 quarter. In total, 179 (51.0%) patients remained on high-dose ICS (≥ 500 $\mu\text{g/day}$ FP-equivalent) throughout the follow-up period and 31 (8.8%) patients were receiving non-high-dose ICS for all four quarters of the follow-up period. There was a stepwise decrease in the proportion of patients on high-dose ICS during each quarter of the follow-up, decreasing from 100% at baseline to 79.8% in quarter 1, and 65.5% in quarter 4 (**Figure 2**).

The proportion of patients with chronic OCS use (≥ 10 mg/day) and the proportion of patients with ≥ 1 OCS burst during follow-up were lower among patients who had discontinued ICS (3.4–9.2% and 14.9–20.8%, respectively) than among those who remained on high-dose ICS (13.9–16.8% and 19.7–26.1%, respectively) in each quarter (**Figure 3A and 3B**). During quarters 1 and 2, the proportion of patients with ≥ 1 exacerbation was broadly similar among patients who discontinued ICS (25.0% and 24.1%, respectively) and those who remained on high-dose ICS (26.4% and 23.9%, respectively) (**Figure 3C**). However, during quarters 3 and 4, a lower proportion of patients experienced ≥ 1 exacerbation in the discontinued ICS group (16.9% and 20.3%, respectively) compared with those remaining on high-dose ICS (27.2% and 27.7%) group (**Figure 3C**). Across all quarters and subgroups, the highest proportion of patients experienced ≥ 1 exacerbation in the ICS dose decrease group in quarter 3 (41.7%) (**Figure 3C**). In quarter 1, the proportion of patients with ≥ 1 SABA claim was slightly higher among patients who discontinued ICS (54.2%) than patients who remained on high-dose ICS (46.8%), but in later quarters a lower proportion of patients discontinuing ICS (35.4–41.4%) had ≥ 1 SABA claim compared with patients remaining on high-dose ICS (43.3–49.0%) or increasing ICS dose (42.3–66.7%) (**Figure 3D**).

Among patients who had discontinued ICS in each quarter, chronic OCS use, the occurrence of exacerbations and SABA claims in the quarter of no ICS use and the prior quarter were investigated. As shown in **Figure 4**, the highest proportion of patients with these outcomes was observed in the last 90 days of baseline; of the 48 patients who discontinued ICS in quarter 1, 25.0%, 58.3%, and 60.4% had chronic OCS use (≥ 10 mg/day), ≥ 1 exacerbation, ≥ 1 SABA claim, respectively, in the quarter prior to initiating mepolizumab treatment. Of patients who discontinued or remained off ICS in quarters 2, 3, or 4, the proportion who had chronic OCS use, exacerbations or SABA claims in the prior quarter was lower than that of patients who discontinued in quarter 1.

24-month follow-up period (post hoc analysis)

Of the 351 patients included in the study, 179 patients were identified with a minimum of 24 months of continuous enrollment after the index date. The stepwise increase in the proportion of patients discontinuing ICS or reducing ICS dose each quarter after initiating mepolizumab was sustained over the 24-month follow-up period (quarters 1–4: 19.6–35.8%, quarters 5–8: 39.1–43.0%; **Figure 5**). In total, 95 (53.1%) patients discontinued ICS for at least 1 quarter of the 24-month follow-up period and 122 (68.2%) patients discontinued or reduced ICS dose for at least 1 quarter. Additionally, whilst 57 (31.8%) patients remained on high-dose ICS for all 8 quarters, 100 (55.9%) patients discontinued or reduced ICS for multiple quarters and 4 (2.2%) patients had no ICS use during any quarter.

Of 90 patients who discontinued ICS at any time during quarters 1–7, 49 (54.4%) patients had ≤ 20 mepolizumab claims and of the 89 patients who did not discontinue ICS, 35 (39.3%) had ≤ 20 mepolizumab claims (**Table 3**). The mean [SD] number of mepolizumab claims was also lower among patients who discontinued ICS than among those who did not (17.7 [9.1] vs 21.0 [7.6]; **Table 3**). Additionally, the proportion of patients who had a SABA claim and the mean number of SABA claims was higher among patient with ≤ 20 mepolizumab claims than among those with > 20 mepolizumab claims, both among patients who discontinued ICS and those who did not with a similar pattern observed for exacerbations. However, proportion of patients who had ≥ 1 exacerbation or a SABA claim were similar among those who discontinued ICS (71.1 % and 95.9%, respectively) and those who did not (79.8% and 94.3%; **Table 3**).

Discussion

This real-world study characterized changes in ICS use and clinically relevant outcomes following initiation of mepolizumab treatment in patients receiving high-dose ICS for severe

eosinophilic asthma. The results demonstrate a stepwise quarter-by-quarter decrease throughout the first year in the proportion of patients on high-dose ICS after initiating treatment with mepolizumab, which was maintained during the second year of observation. This is largely consistent with the results of a systematic review of real-world studies of omalizumab in the treatment of asthma, which found that 48.1% of patients reduced or discontinued ICS at 12-months and this increased with time on omalizumab.²⁵

In all, 49% of patients discontinued or reduced ICS for at least 1 quarter of the 12-month follow-up period and 53% of the 24-month follow-up cohort were able to discontinue ICS for at least 1 quarter. Whilst a considerable proportion of patients cycled between ICS dosage categories each quarter, the net number of patients on high-dose ICS decreased with time from 100% at baseline to 66% at quarter 4, and was sustained over 24 months of mepolizumab treatment. It should be noted that only a small proportion of patients discontinued ICS entirely for the duration of the follow-up. However, given the broad anti-inflammatory action of corticosteroids and role in asthma treatment, the appropriateness of complete cessation of ICS in patients receiving biologics targeting specific anti-inflammatory pathways such as interleukin-5 is yet to be determined.

Overall, the results presented here suggest that for patients with severe eosinophilic asthma, reductions in ICS use may be more feasible after treatment with mepolizumab for at least 3 months and that the longer patients continue mepolizumab treatment, the more likely they are to reduce ICS use. This is supported by the continued reduction in the number of patients on high-dose ICS over quarters 5–8 of the 24-month follow-up. This aligns with both real-world observations of reductions in OCS usage following mepolizumab initiation and the results of clinical and real-world studies, which have also demonstrated a greater reduction in OCS usage with length of time on mepolizumab treatment.^{13, 22} In the current study, the quarterly

decreases in the proportion of patients receiving high-dose ICS and the regular flow of patients between dosage groups (in both directions) reinforce the importance of regular monitoring and review of ICS dose requirements for patients with severe eosinophilic asthma. This is in accordance with the GINA 2020 statement, which supports the use of an asthma action plan providing personalized guidance for the individual patient to make medication adjustments, particularly in ICS dose.²⁶

The results also indicate a decreased frequency of exacerbations and SABA use, among those who discontinued or reduced ICS after initiating mepolizumab, particularly in the latter 2 quarters of the 12-month follow-up period. This is consistent with clinical studies, which have also demonstrated improved asthma control over time with mepolizumab versus placebo.^{13, 16, 27} The results of the current study (reduced exacerbation rate, SABA use, and OCS use) also suggest that the reduction in ICS use may act as a proxy for improved disease control, which would be expected to increase with time on mepolizumab therapy. However, it should be noted that no statistically significant differences were observed with exacerbation frequency and SABA use in patients who discontinued ICS and those who remained on ICS in the 24-month follow-up analysis. This lack of difference may be due to patients who discontinued ICS having fewer mepolizumab claims than those who did not, indicating worse adherence or may be due to the sample size of groups in this analysis.

Notably, patients who reduced their ICS use were also able to reduce OCS use. The chronological order in which ICS and OCS dose reductions took place was not investigated; however, current asthma management guidelines for physicians reinforce the importance of reducing the OCS dose followed by reductions in ICS.²⁶ However, while the short- and long-term adverse effects of corticosteroids are well established²⁻⁴, sustained exposure to high-dose ICS may also contribute to the overall systemic burden and adverse effects of corticosteroids

in patients with asthma, and, as such, ICS is also an important target for reducing corticosteroid exposure. There is also evidence that systemic absorption of ICS is greater when asthma is controlled than in individuals with airflow obstruction⁴, suggesting that treatment with biologics may actually increase ICS toxicity. The potential for adverse impacts of corticosteroids reinforces the importance of regular monitoring of disease control and ICS dosage after initiating biologic treatment and is in line with asthma management guidelines to review response 3–6 months after interventions to optimize management.¹¹

As we employed a database analytic approach without access to patient charts, it is not possible to identify whether changes in ICS use were directed by physicians or patients. However, it is possible to derive some information regarding ICS use from patterns of exacerbations, OCS use and SABA use relative to ICS use. Asthma management guidelines recommend considering treatment step down when asthma treatment has been well controlled for 3 months or more, with reductions of ICS doses by 25–50% at 3 month intervals.²⁶ Therefore, it is unlikely that ICS reduction would be advised by a healthcare practitioner (HCP) in patients requiring OCS bursts or SABA or who have experienced a recent exacerbation. HCPs are also unlikely to advocate for a transition from high-dose ICS to complete discontinuation, or immediately following initiation with a biologic. In the current study, the greatest flux from high-dose to no ICS was observed between the baseline period and quarter 1, which may have been patient-led. In subsequent quarters, there was less direct flow between the high and no ICS groups, at which time patients are more likely to have returned to their HCP for consultation.

Suboptimal adherence to both ICS/LABA and biologic treatments has been found to be common among patients with severe asthma²⁸ and this is also supported by our data. Less than 20% of patients had >80% ICS coverage during the baseline period and among the 24-

month follow-up cohort, 54% of patients who discontinued ICS also had suboptimal mepolizumab coverage (<20 claims). Caminata *et al.* looked at adherence rates to ICS/LABA treatment in the 6 months before and after beginning treatment with a biologic and found no significant difference in the proportion of adherent patients, with only approximately 40% of patients having >80% ICS coverage.²⁸ Similarly, Maddux *et al.* found adherence to ICS was similarly low before and after initiating biologic treatment, but that adherence to biologic treatment was significantly higher than ICS.²⁹ Further, a recent real-world study found that patterns of ICS adherence did not change in the 12 months before and after mepolizumab initiation, but that patients with poor adherence had worse clinical outcomes and lower OCS dose reductions than patients with good adherence.²³ Therefore, while low adherence is likely, the extent to which changes in ICS dosage in the current study can be explained by changes in adherence cannot be fully established, particularly as improvements in clinical outcomes with mepolizumab treatment suggest that patients and HCPs may have chosen to step down ICS therapy. Therefore, improved mepolizumab adherence could possibly have augmented further reductions in ICS use, although further studies are required to assess this.

Several limitations of the current study inherent to real-world database studies should be acknowledged. As the study included only patients with private and Medicare insurance, the results may not be generalizable to patients without health insurance or other types of insurance. Additionally, as estimations of drug dose were based solely on claims, they assumed 100% compliance with prescription fills although real-world adherence is likely lower than this. Furthermore, a SABA claim may not be a strong indicator of worsening asthma, for example, inhalers may be lost or used to prevent exercise-induced bronchoconstriction. In order to characterize OCS use a threshold for chronic OCS use of estimated daily OCS dose of 10mg/day was selected. Lower doses of OCS such as 5mg could still be considered clinically relevant and analysis at alternative thresholds may provide

additional insight, however these thresholds were not analyzed during the current analysis. In addition to these considerations, it should be noted that the numbers of patients in the high-dose ICS, reduced ICS, or no ICS subgroups each quarter were not balanced; the high-dose ICS group was consistently the largest. Furthermore, the numbers of patients in some subgroups were small.

The results of this real-world study suggest that reduction in ICS dose or ICS discontinuation is achievable for some patients receiving mepolizumab, although the driving factors for such reductions remain to be determined. The proportion of patients who discontinued ICS or reduced high-dose ICS treatment after starting mepolizumab increased over time, highlighting the need for frequent communication and shared decision-making between HCPs and their patients to manage ICS medication. Future studies are needed to establish an evidence-based foundation for discontinuing or reducing the dose of ICS medications in patients treated with mepolizumab and other biologic medications for severe eosinophilic asthma.

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Tables

Table 1. Minimal-, low-, medium-, and high-dose categories for ICS/LABA combinations and ICS drugs

	Minimal	Low	Medium	High
ICS/LABA combo drug (brand/ generic name)	Strength (µg)*			
Advair		45, 100, 115	230, 250	500
Airduo Respiclick		55, 113	232	
Fluticasone propionate/salmeterol xinafoate		55, 113	232	
Symbicort			80	160
Dulera			100	200
Breo Ellipta			100	200
ICS drug (generic name)	Daily dose (µg)			
Beclomethasone dipropionate (HFA [†])	<100	$100 \leq X \leq 200$	$200 < X \leq 400$	>400
Budesonide	<200	$200 \leq X \leq 400$	$400 < X \leq 800$	>800
Ciclesonide	<80	$80 \leq X \leq 160$	$160 < X \leq 320$	>320
Fluticasone furoate	<100	100	N/A	200
Fluticasone propionate	<100	$100 \leq X \leq 250$	$250 < X \leq 500$	>500
Mometasone furoate	<110	$110 \leq X \leq 220$	$220 < X \leq 440$	>440
Triamcinolone acetonide	<400	$400 \leq X \leq 1000$	$1000 < X \leq 2000$	>2000

Low, medium and high doses are as defined in Global Initiative for Asthma, Global Strategy for Asthma Management and Prevention, 2018.²⁴ Minimal doses are those less than 'low'.

*Strength refers to the strength of ICS component in the drug, per single actuation;

[†]chlorofluorocarbon containing inhalers were gradually being phased out and replaced with HFA-based alternatives around 2000.

ICS, inhaled corticosteroids; OCS, oral corticosteroids; LABA, long-acting β_2 -agonist; HFA, hydrofluoroalkanes.

Table 2. Patient demographics and clinical characteristics during the baseline period

	All patients (N=351)
Age, years, mean (SD)	52.1 (12.2)
Age category, years, n (%)	
12–17	7 (2.0)
18–34	21 (6.0)
35–44	50 (14.0)
45–54	100 (28.0)
55–64	144 (41.0)
≥65	29 (8.0)
Female, n (%)	219 (62.0)
Geographic region, n (%)	
Northeast	73 (21.0)
North Central	81 (23.0)
South	140 (40.0)
West	56 (16.0)
Unknown	1 (0.0)
Deyo-Charlson Comorbidity Index, mean (SD)	1.4 (1.0)
Comorbid conditions, n (%)	
Allergic rhinitis	251 (71.5)
Atopic dermatitis	12 (3.4)
Chronic idiopathic urticaria	3 (0.9)
Chronic obstructive pulmonary disease	110 (31.3)

Diabetes	38 (10.8)
Eosinophilic esophagitis	5 (1.4)
Eosinophilic granulomatosis with polyangiitis	13 (3.7)
Gastroesophageal reflux disease	122 (34.8)
Hypertension	138 (39.3)
Nasal polyps	1 (0.3)
Respiratory infections	75 (21.4)
Rheumatoid arthritis	5 (1.4)
Sinusitis	200 (57.0)
Acute	123 (35.0)
Chronic	150 (42.7)
Systemic lupus erythematosus	1 (0.3)
Respiratory-related symptoms or procedures (%)	
Dyspnea	155 (44.2)
Stridor	1 (0.3)
Cough	155 (44.2)
Wheezing	58 (16.5)
Other respiratory symptoms	114 (32.5)
Pulmonary function test	327 (93.2)
Chest X-rays	222 (63.2)
Pneumonia/influenza	51 (14.5)
Other respiratory infections	163 (46.4)

SD, standard deviation.

Table 3. Outcomes during the 24-month follow-up period

	Discontinued ICS at any time N=90	Did not discontinue ICS* N=89	p-value
All patients			
Number of mepolizumab claims per patient			
Mean (SD)	17.7 (9.1)	21.0 (7.6)	0.008
Median (IQR)	19.0 (10.0, 23.0)	22.0 (17.0, 25.0)	
Patients with ≥ 1 exacerbation, n (%)	64 (71.1)	71 (79.8)	0.178
Number of exacerbations per patient, mean (SD)	2.1 (2.2)	2.2 (2.3)	0.711
Patients with ≥ 1 SABA claim, n (%)	83 (92.2)	81 (91.0)	0.770
Number of SABA claims per patient, mean (SD)	6.8 (8.3)	8.1 (11.1)	0.350
Patients with ≤ 20 mepolizumab claims, n (%)	49 (54.4)	35 (39.3)	0.043
Number of mepolizumab claims per patient			
Mean (SD)	11.3 (5.6)	14.2 (5.6)	0.023
Median (IQR)	11.0 (7.0, 17.0)	17.0 (10.0, 19.0)	
Patients with ≥ 1 exacerbation, n (%)	36 (73.5)	31 (88.6)	0.089
Number of exacerbations per patient, mean (SD)	2.4 (2.3)	2.6 (2.4)	0.701
Patients with ≥ 1 SABA claim, n (%)	47 (95.9)	33 (94.3)	1.000
Number of SABA claims per patient, mean (SD)	8.7 (9.9)	8.9 (12.7)	0.961
Patients with > 20 mepolizumab claims, n (%)	41 (45.6)	54 (60.7)	0.043
Number of mepolizumab claims per patient			
Mean (SD)	25.3 (6.2)	25.5 (5.0)	0.886

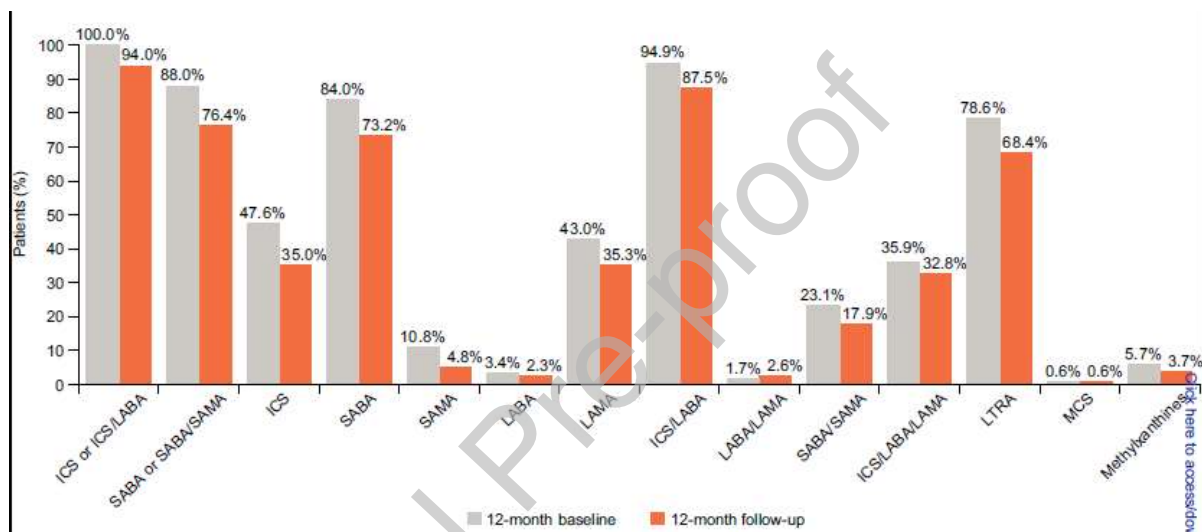
Median (IQR)	24.0 (22.0, 25.0)	25.0 (23.0, 26.0)	
Patients with ≥ 1 exacerbation, n (%)	28 (68.3)	40 (74.1)	0.536
Number of exacerbations per patient, mean (SD)	1.7 (2.1)	2.0 (2.2)	0.573
Patients with ≥ 1 SABA claim, n (%)	36 (87.8)	48 (88.9)	1.000
Number of SABA claims per patient, mean (SD)	4.4 (4.8)	7.6 (10.0)	0.057

*Includes 5 patients who discontinued ICS during the final quarter (quarter 8) of follow-up.

ICS, inhaled corticosteroid; IQR, interquartile range; SABA, short-acting β_2 -agonist; SD, standard deviation.

Figure Legend

Figure 1. Use of asthma medications during 12-month baseline and 12-month follow-up periods; before and after initiating treatment with mepolizumab



ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MCS, mast cell stabilizers; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist.

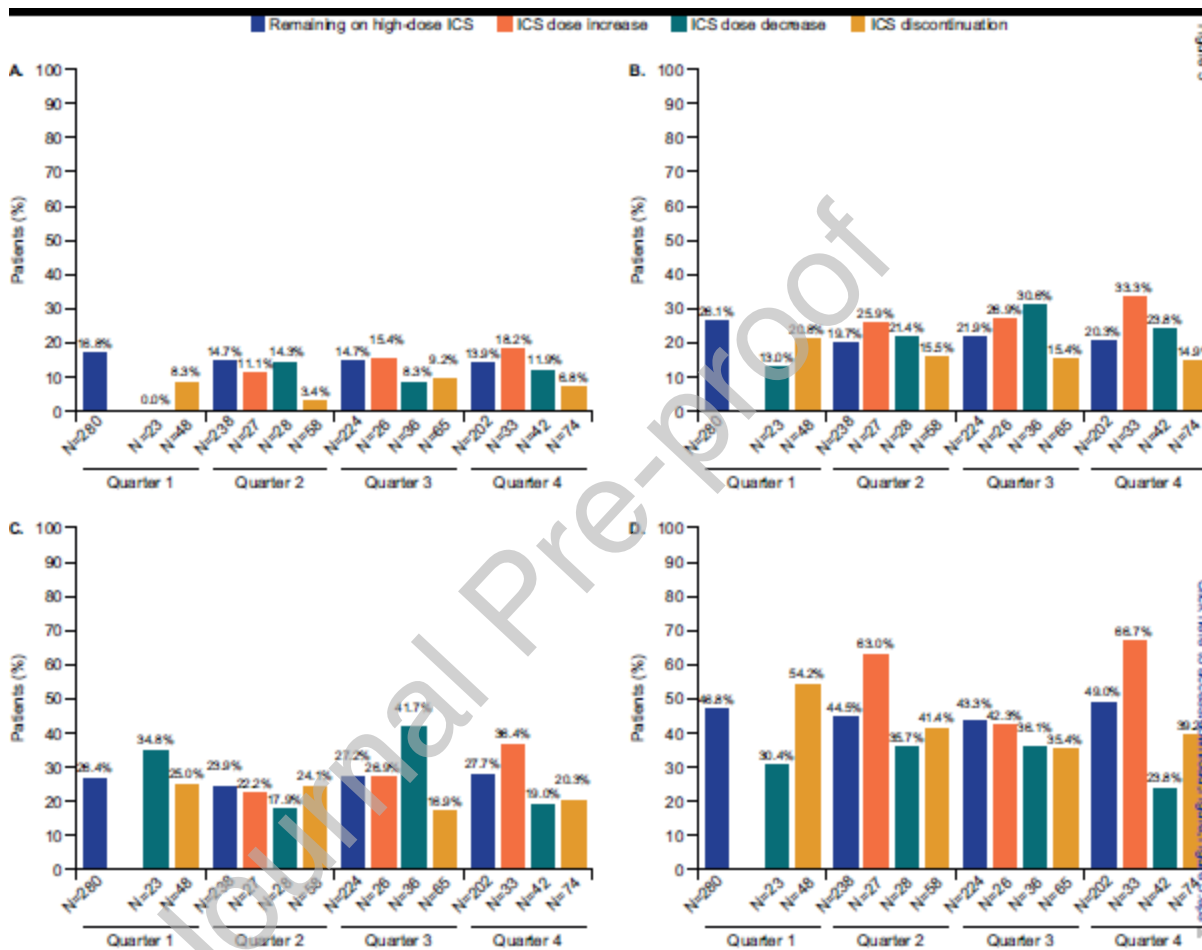
Figure 2. Quarterly changes in ICS use during the 12-month follow-up period; proportion of patients receiving high dose ICS, other dose ICS or no ICS each quarter



High ICS dose ≥ 500 $\mu\text{g/day}$ FP-equivalent; Other ICS dose included low or medium (< 500 $\mu\text{g/day}$ FP-equivalent) ICS/LABA combination drug dose, or minimal-, low-, or medium-dose ICS (< 500 $\mu\text{g/day}$ FP-equivalent) as described in Table 1.

FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist.

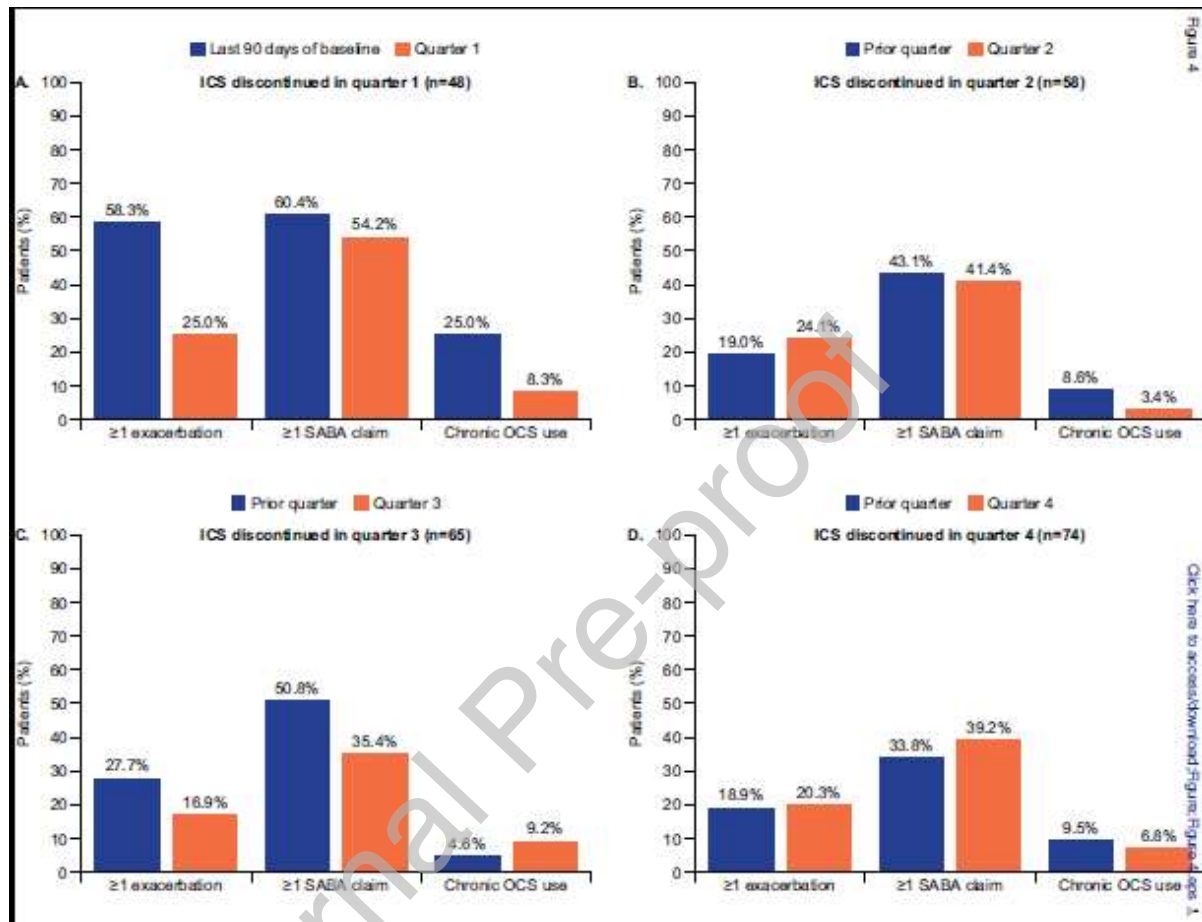
Figure 3. Proportion of patients with A) chronic OCS use*, B) ≥ 1 OCS burst, C) ≥ 1 exacerbation, and D) ≥ 1 SABA claim for patients who remained on high dose ICS, increased ICS dose, decreased ICS dose, and discontinued or continued on no ICS in each quarter of follow-up



*Mean daily OCS dose of ≥ 10 mg prednisone equivalent throughout a given 3-month quarter.

ICS, inhaled corticosteroid; OCS, oral corticosteroid; SABA, short-acting β_2 -agonist

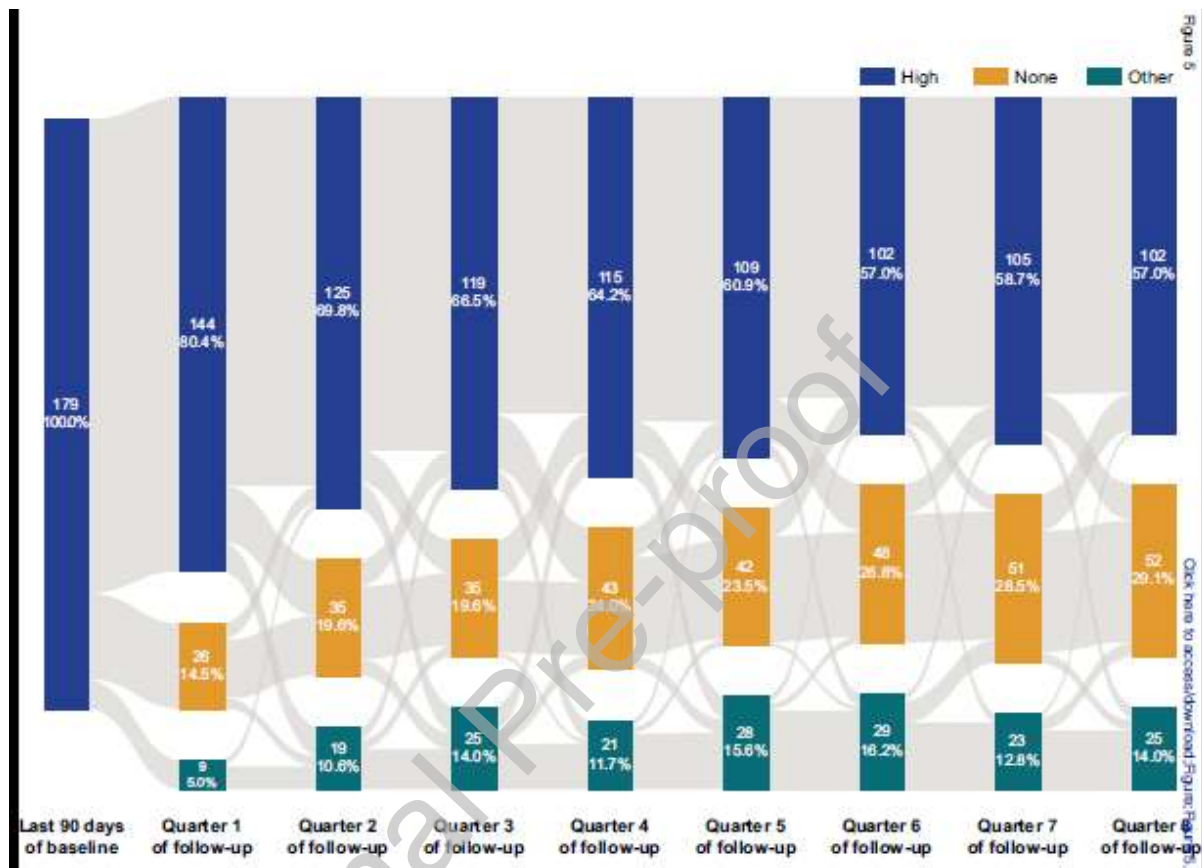
Figure 4. Proportion of patients with ≥ 1 exacerbation, chronic OCS use* and ≥ 1 SABA claim in the quarter of discontinuing ICS and quarter prior to discontinuing ICS in A) quarter 1, B) quarter 2, C) quarter 3, and D) quarter 4



*Mean daily OCS dose of ≥ 10 mg prednisone equivalent throughout a given 3-month quarter.

ICS, inhaled corticosteroids; OCS, oral corticosteroids; SABA, short-acting β_2 -agonist.

Figure 5. Quarterly changes in ICS use during 24-month follow-up period; proportion of patients receiving high dose ICS, other dose ICS or no ICS each quarter



High ICS dose ≥ 500 $\mu\text{g/day}$ FP-equivalent; Other ICS dose included low or medium (< 500 $\mu\text{g/day}$ FP-equivalent) ICS/LABA combination drug dose, or minimal-, low-, or medium-dose ICS (< 500 $\mu\text{g/day}$ FP-equivalent) as described in Table 1.

FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist.