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ORIGINAL RESEARCH

Real-World Effectiveness of Mepolizumab in Patients with Allergic and Non-Allergic Asthma

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Purpose: Real-world data on mepolizumab in patients with severe asthma and allergic and non-allergic phenotypes are limited. This study investigated the effectiveness of mepolizumab treatment in patients with severe asthma with allergic and non-allergic phenotypes.

Patients and Methods: This retrospective cohort study (GSK ID: 214148) used administrative claims data from the Optum Research Database. Eligible patients were ≥6 years of age with asthma and had ≥2 mepolizumab claims post-index. Index date was the first mepolizumab claim/administration (January 2016–December 2018). Patients were divided into two cohorts: allergic and non-allergic asthma, based on diagnosis codes, medication use and lab test results. Outcomes included the rate of asthma-related exacerbations and oral corticosteroid (OCS) use during the 12 months before (baseline period) and 12 months after (follow-up period) mepolizumab initiation. Study ended in December 2019.

Results: Overall, 240 (44.6%) and 298 (55.4%) patients were included in the allergic and non-allergic asthma cohorts, respectively. Mean (standard deviation [SD]) counts of asthma-related exacerbations were significantly reduced from baseline to follow-up in both the allergic and non-allergic asthma cohorts (3.2 [2.5] to 2.1 [2.1], $p < 0.001$ and 2.5 [2.2] to 1.7 [1.9], $p < 0.001$, respectively). The mean number of OCS pharmacy claims was significantly decreased by 33.3% and 41.4% from baseline to follow-up in the allergic and non-allergic cohorts, respectively ($p < 0.001$); mean daily OCS dose significantly decreased by 30.6% and 45.4%, respectively ($p < 0.001$) as well as the mean number of OCS bursts, which decreased by 44.9% and 41.8%, respectively ($p < 0.001$). No significant differences were observed between cohorts in reductions in asthma exacerbations, counts of OCS pharmacy claims or OCS bursts (baseline to follow-up).

Conclusion: Mepolizumab significantly reduced asthma exacerbations and OCS use in patients with allergic and non-allergic asthma, suggesting that mepolizumab provides real-world benefit in severe asthma irrespective of whether a patient has an allergic phenotype.

Keywords: severe asthma, phenotype, exacerbation, oral corticosteroid

Introduction

Severe asthma is characterized by treatment with high-dose inhaled corticosteroids (ICS) in addition to a second controller and/or systemic corticosteroids (SCS), including oral corticosteroids (OCS).[1] However, symptoms may remain uncontrolled leading to frequent asthma exacerbations requiring short-acting $ß_2$-agonist (SABA) and OCS use, emergency treatment, or hospitalization.[1,2] Severe asthma can be classified by phenotype including those with elevated sputum and/or blood eosinophil counts (severe asthma with an eosinophilic phenotype) or sensitivity to environmental allergens plus elevated immunoglobulin E (IgE) levels (severe allergic asthma).[3–5] These phenotypes share features including being mechanistically driven by type 2 inflammation and the presence of elevated eosinophil counts.[5] Approximately three-quarters of patients with severe asthma with an eosinophilic phenotype also have an allergic phenotype.[6] Treatments targeting the common mechanisms underlying phenotypes, such as elevated eosinophil counts, plausibly provide benefit across asthma phenotypes.[5]

Mepolizumab is a humanized monoclonal antibody approved in Europe and the USA as an add-on therapy for the treatment of severe asthma.[7,8] By specifically targeting interleukin (IL)-5, a cytokine that promotes differentiation, activation, and eosinophil survival, mepolizumab enables a precision medicine approach to eosinophilic disease.[9–11] Mepolizumab

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efficacy in patients with severe asthma is well documented in clinical trials,[12–14] post hoc analyses of clinical trials,[15,16] and real-world studies.[17–20] However, most data on mepolizumab efficacy in patients with and without allergic phenotypes is limited to clinical studies. Post hoc analyses of the DREAM (NCT01000506), MENSA (NCT01691521), and MUSCA (NCT02281318) clinical trials demonstrated similar clinical benefit of mepolizumab in patients with severe asthma irrespective of atopic status, prior omalizumab use, IgE level and sensitivity to particular allergens.[15,16,21–23] Nearly all patients who had prior anti-IgE therapy, omalizumab in the prospective OSMO trial (NCT02654145) demonstrated clinical benefit with mepolizumab.[24,25]

Real-world data inclusive of prospective trials, electronic health records, and databases can provide insights into medication effectiveness in a more representative population than the tightly controlled clinical trial setting.[26] Real-world comparative mepolizumab data in allergic and non-allergic asthma are limited to two retrospective studies among patients with severe asthma and comorbidities including allergic disease.[27,28] As such, further real-world data on clinically relevant outcomes in patients with severe asthma and different allergic phenotypes are needed. This real-world study investigated mepolizumab effectiveness in patients with allergic and non-allergic asthma through assessment of asthma exacerbation rates, OCS, and SABA utilization.

Materials and Methods

Study Design

This was a retrospective, real-world, cohort study (GSK ID: 214148) of administrative claims data from the Optum Research Database (ORD) from January 1, 2011 to December 31, 2019 (study period; Figure 1). This fully de-identified US-based database comprised medical and pharmacy claims of over 111 million people since 1993.[29] Eligible patients were identified on the date of their first mepolizumab pharmacy fill/administration (index date) between January 1, 2016 and December 31, 2018 (identification period). The 12 months preceding and after index were the baseline and follow-up periods, respectively. A variable length look-back period (≥12 and ≤60 months) preceding the index date was used for cohort assignment; this period's length was determined by each patient's length of continuous enrollment.

Eligibility Criteria

Included patients had ≥1 pharmacy or medical claims for mepolizumab (indicating treatment initiation) during the identification period, had continuous enrollment with medical and pharmacy coverage during the baseline and follow-up periods, were ≥6 years of age during the index year, had ≥1 non-diagnostic medical claim (ie, excluding lab and imaging tests that may be used to rule out asthma) with a diagnosis code for asthma in the primary position during baseline, and had ≥2 mepolizumab claims on separate dates during first 180 days of follow-up (including the index date). Patients were excluded if they had ≥1 mepolizumab pharmacy fill or infusion during the baseline period (excluding the index date), ≥1

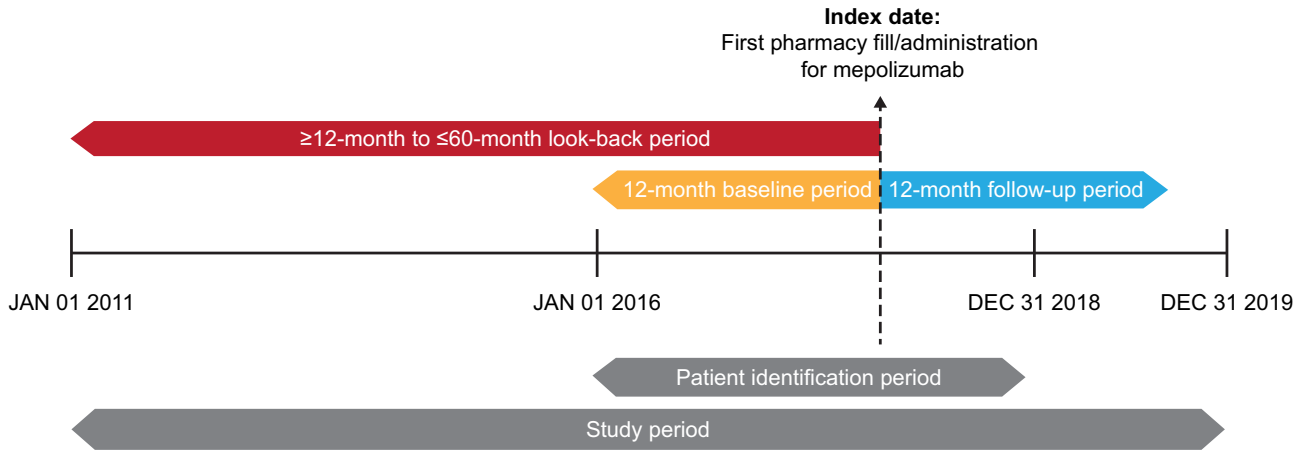

Figure 1 Study design.

pharmacy fill or infusion for reslizumab, benralizumab or dupilumab during the baseline or follow-up periods, ≥1 pharmacy fill or infusion for omalizumab during the follow-up period (omalizumab use during the baseline period was used for cohort identification), or had missing values for gender or geographic region.

Patients were categorized into cohorts based on the presence or absence of allergic asthma (allergic asthma and non-allergic asthma cohorts). The allergic asthma cohort included patients who had ≥1 of the following: 1) medical claim for immunotherapy, 2) pharmacy fill or administration of omalizumab with no diagnosis for urticaria, 3) a diagnosis code for allergic asthma plus a positive specific IgE serum test (≥0.35 kU/L), or 4) a diagnosis code for allergic asthma plus ≥1 diagnosis code for an expected or common comorbidity. Eligible allergic comorbidities included allergic rhinitis, conjunctivitis, chronic urticaria, atopic dermatitis, food allergies, anaphylaxis, eosinophilic esophagitis, and chronic sinusitis. Patients were excluded from the allergic asthma cohort if they had ≥1 diagnosis code for intrinsic asthma. The non-allergic asthma cohort included patients who did not meet the allergic asthma cohort criteria.

Variables/Outcomes

Study variables and outcomes included demographics at index (or the first claim following the index date), clinical characteristics during the baseline period, the asthma-related exacerbations annual rate (primary outcome), counts of unique mepolizumab administration dates at index and during follow-up, OCS use and SABA utilization (both secondary outcomes) during the baseline and follow-up periods. Demographics assessed included age, gender, and race/ethnicity. Baseline clinical characteristics included Charlson comorbidity index (CCI) score, and comorbidities. Asthma-related exacerbations were defined as ≥1 outpatient or emergency department (ED) claim with a diagnosis of asthma in any position and ≥1 pharmacy or medical claim for SCS (intramuscular, intravenous, or oral) within ±5 days, or an inpatient hospitalization with a primary diagnosis of asthma (at any time during hospitalization). Exacerbations on the index date were considered baseline exacerbations. Claims for scheduled administrations of mepolizumab were excluded from outpatient encounters used to identify exacerbations. Exacerbation episodes within 14 days of the end of the previous exacerbation episode were considered single events.

OCS use outcomes during the baseline and follow-up periods included the proportion of patients with any OCS use, the number of OCS claims per patient, mean daily OCS dose, the mean number of OCS bursts, and number of patients with chronic OCS use. Mean daily OCS use was calculated as prednisone equivalents using pharmacy claims. OCS bursts were defined as average daily dose ≥20 mg prednisone equivalent for 3–28 days and ≥1 outpatient or ED claim with a diagnosis of asthma within ±7 days. Patients with chronic OCS use were defined as those with ≥10 mg/day prednisone equivalent use during each quarter of the follow-up period who also had chronic OCS use during the baseline period (≥10 mg/day prednisone equivalent in the 90 days pre-index). SABA use outcomes included the proportion of patients with SABA use and the number of canisters dispensed (based on the ratio of quantity to package size).

Statistical Analysis

Study variables were analyzed descriptively and presented as mean (standard deviation [SD]) for continuous variables and number (proportion) for categorical variables. Results were presented separately for each cohort during the baseline and follow-up periods. Bivariate analyses were tested for differences in outcomes between cohorts, with Chi-square tests used for categorical variables, and Student's t-tests or Wilcoxon rank sum tests used for continuous variables. Following review of descriptive results, difference-in-difference (DiD) analyses to measure relative change in number of events (baseline to follow-up) between patients in both cohorts, were performed for count of exacerbations, proportion of patients with OCS use, OCS daily dose, count of OCS claims, number of OCS bursts, proportion of patients with SABA use, and count of SABA canisters.

Results

Patient Population

In total the study included 538 patients, of whom 240 (44.6%) and 298 (55.4%) were allocated into the allergic asthma and non-allergic asthma cohorts, respectively (Supplementary Figure 1). The mean (SD) age was significantly lower in

patients with allergic asthma compared with non-allergic asthma (54.8 [15.7] vs 59.1 [14.3]; p < 0.001; Table 1). Most patients were female, and a greater proportion were female in the allergic asthma cohort versus the non-allergic asthma cohort (65.4% vs 58.1%; p = 0.091). There was no significant difference between cohorts in ethnicity, CCI score, and OCS and SABA use at baseline (Table 1).

The most common comorbidities reported in ≥5% of patients in both cohorts at baseline were allergic rhinitis, chronic obstructive pulmonary disease (COPD), sinusitis, and nasal polyps (Figure 2). Significantly more patients in the allergic versus non-allergic asthma cohort had allergic rhinitis (53.8% vs 23.8%; p < 0.001), sinusitis (37.5% vs 28.2%; p = 0.026), and eosinophilic esophagitis (2.5% vs 0.3%; p = 0.049), and fewer patients had COPD (20.8% vs 35.6%; p < 0.001; Figure 2).

Table 1 Baseline Demographics and Clinical Characteristics

	Allergic Asthma (n=240)	**Non-Allergic Asthma (n=298)**	**p-value**
Age, years, mean (SD)	54.8 (15.7)	59.1 (14.3)	**< 0.001**
Age group, years, n (%)			**< 0.001**
6–17	9 (3.8)	3 (1.0)	**0.040**
18–44	43 (17.9)	45 (15.1)	0.413
45–64	127 (52.9)	126 (42.3)	**0.015**
≥65	61 (25.4)	124 (41.6)	**< 0.001**
Female, n (%)	157 (65.4)	173 (58.1)	0.091
Race/ethnicity, n (%)			0.729
White	154 (64.2)	185 (62.1)	0.654
African American/Black	29 (12.1)	29 (9.7)	0.404
Asian	5 (2.1)	10 (3.4)	0.438
Hispanic	18 (7.5)	25 (8.4)	0.751
Unknown	34 (14.2)	49 (16.4)	0.549
CCI score, mean (SD)	1.6 (1.2)	1.7 (1.2)	0.748
CCI score, n (%)			0.940
0	0 (0.0)	0 (0.0)	–
1–2	190 (79.2)	232 (77.8)	0.752
3–4	40 (16.7)	53 (17.8)	0.819
5+	10 (4.2)	13 (4.4)	1.000
Baseline OCS use			
Any use, n (%)	217 (90.4)	272 (91.3)	0.764
OCS daily dose (mg/day), mean (SD)	4.9 (4.9)	5.6 (5.2)	0.104
Baseline SABA use			
Any use, n (%)	202 (84.2)	262 (87.9)	0.211
Count of SABA canisters, mean (SD)	5.0 (6.2)	5.7 (6.5)	0.207

Notes: p-values that reached statistical significance are indicated in bold.
Abbreviations: CCI, Charlson comorbidity index; OCS, oral corticosteroid; SABA, short-acting ß$_2$-agonist; SD, standard deviation.

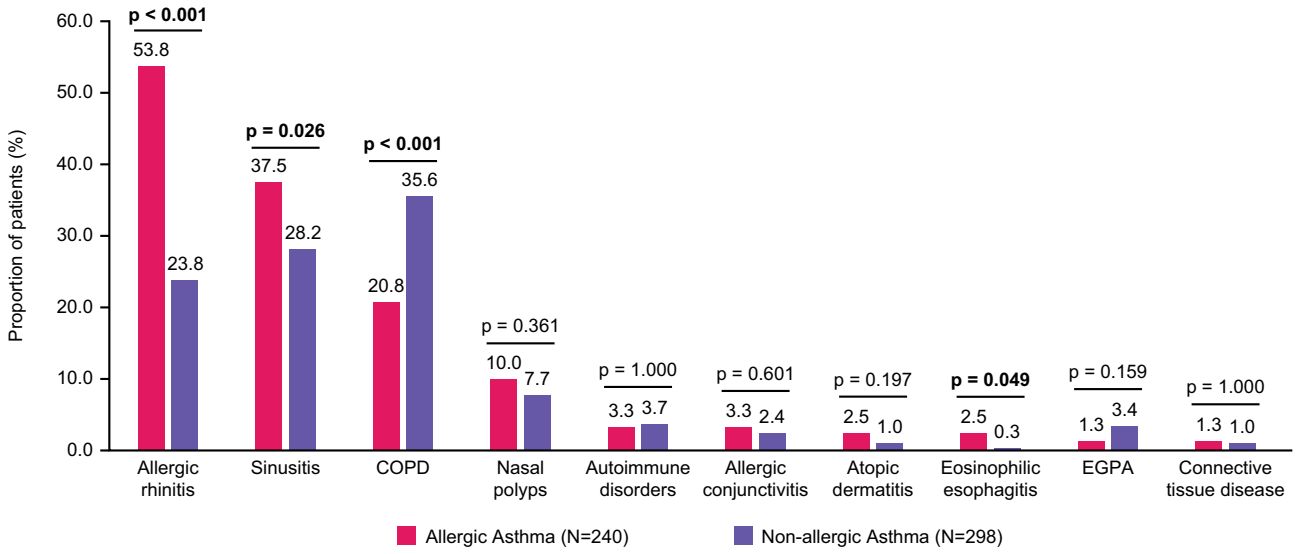

Figure 2 Proportion of patients with select comorbidities at baseline. p-values that reached statistical significance are indicated in bold.
Abbreviations: COPD, chronic obstructive pulmonary disease; EGPA, eosinophilic granulomatosis with polyangiitis.

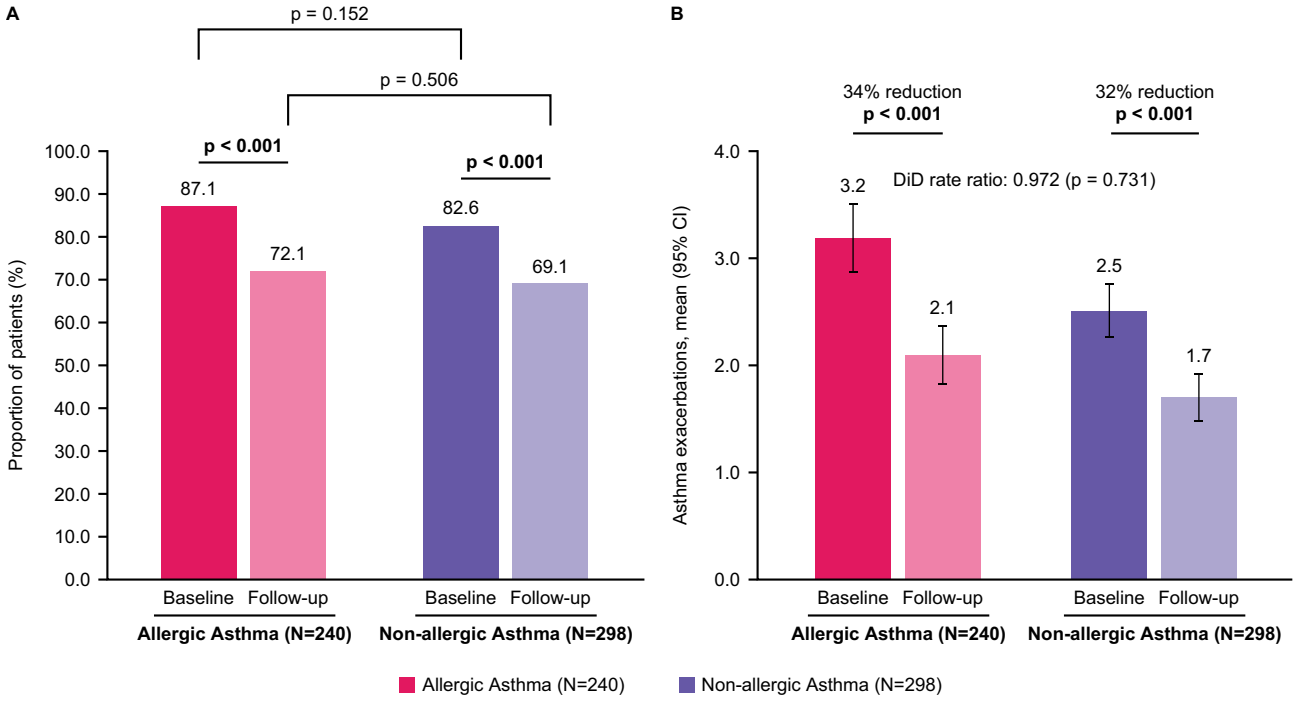

Figure 3 Rate of asthma exacerbations: (**A**) Proportion of patients with ≥1 asthma exacerbation during baseline and follow-up; (**B**) Change in mean count of asthma exacerbations between baseline and follow-up. p-values that reached statistical significance are indicated in bold.
Abbreviations: CI, confidence interval; DiD, difference-in-difference.

Asthma-Related Exacerbations

No statistically significant difference existed between cohorts in the proportion of patients with asthma-related exacerbations during the baseline and follow-up periods (Figure 3A). When comparing baseline and follow-up periods, there was a 17.2% and 16.3% decrease in the proportion of patients with asthma exacerbations in the allergic and non-allergic asthma cohorts, respectively (no statistical testing performed; Figure 3A).

The mean (SD) rate of asthma-related exacerbations was significantly higher in patients with allergic versus non-allergic asthma during the baseline (3.2 [2.5] vs 2.5 [2.2]; p < 0.001) and follow-up (2.1 [2.1] vs 1.7 [1.9]; p = 0.022) periods. When comparing the baseline and follow-up periods, there was a 34.1% and 32.2% decrease in the mean number of asthma-related exacerbations from the baseline to follow-up period in both the allergic asthma and non-allergic asthma cohorts, respectively (both p < 0.001; Figure 3B). No statistically significant difference existed between allergic asthma and non-allergic asthma cohorts in the decreases in asthma exacerbations (DiD rate ratio [RR]=0.972; p = 0.731; Figure 3B).

Mepolizumab Administrations

During the follow-up period, the mean (SD) count of unique mepolizumab administration dates were similar across the allergic and non-allergic cohorts, with 11.0 (5.4) and 10.8 (4.5) administrations, respectively (including the index administration).

OCS and SABA Use

During the baseline period, 90.4% and 91.3% of patients in the allergic asthma and non-allergic asthma cohorts, respectively, had ≥1 OCS claim. The proportion of patients with any OCS use significantly decreased from the baseline to follow-up period by 16.1% and 17.3% in the allergic and non-allergic asthma cohorts (p < 0.001), respectively; there was no difference between cohorts in this reduction (DiD RR = 1.129, p = 0.694; Table 2). The mean (SD) number of OCS pharmacy claims in the baseline period was similar in the allergic and non-allergic asthma cohorts (5.2 [4.5] vs 5.5 [4.1]) but significantly decreased by 33.3% and 41.4%, respectively, during the follow-up period (p < 0.001). No difference was observed between cohorts in the decrease in the mean count of OCS pharmacy claims from baseline to follow-up (DiD RR = 1.136, p = 0.104; Figure 4A). In addition, mean daily OCS dose significantly decreased by 30.6% and 45.4% from baseline to the follow-up period for the allergic and non-allergic asthma cohorts, respectively (p < 0.001; Table 2). The difference in the decrease in mean OCS daily dose from baseline to follow-up was significant between the cohorts (DiD RR = 1.272, p = 0.008).

During the baseline period, patients in the allergic and non-allergic cohorts had similar mean (SD) counts of OCS bursts (0.8 [1.3] vs 0.7 [1.4]); this was significantly reduced by 44.9% and 41.8%, respectively, during the follow-up period (p < 0.001; Figure 4B). No significant difference existed between cohorts in the decrease in the mean count of

Table 2 OCS Daily Dose During Baseline and Follow-Up Among All Patients

	Allergic Asthma (n=240)	**Non-Allergic Asthma (n=298)**
Proportion of patients with ≥1 OCS claim, n (%)		
Baseline period	217 (90.4)	272 (91.3)
Follow-up period	182 (75.8)	225 (75.5)
Baseline to follow-up period difference p value	< 0.001	< 0.001
Difference in difference, RR (p-value)	1.129 (p = 0.694)	
OCS daily dose, mean (SD)		
Baseline period	4.9 (4.9)	5.6 (5.2)
Follow-up period	3.4 (5.0)	3.1 (4.3)
Baseline to follow-up period difference p-value	< 0.001	< 0.001
Difference in difference, RR (p-value)	1.272 (**p = 0.008**)	

Notes: p-values that reached statistical significance are indicated in bold.
Abbreviations: OCS, oral corticosteroid; RR, rate ratio; SD, standard deviation.

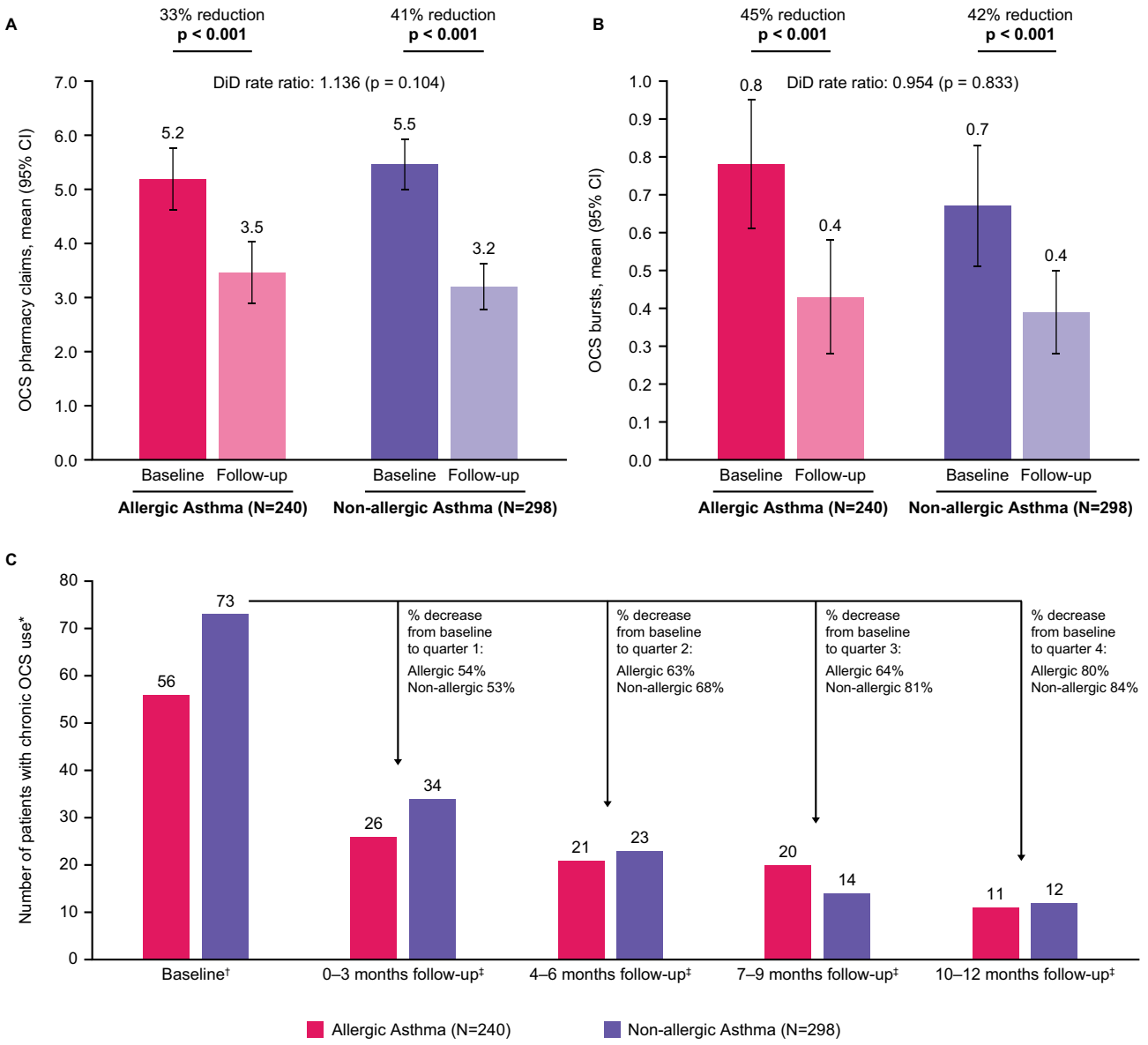

Figure 4 OCS use: (**A**) Mean count of OCS pharmacy claims; (**B**) Mean count of OCS bursts; (**C**) Number of patients with chronic OCS use. p-values that reached statistical significance are indicated in bold. *Pre-index counts (ie from Baseline period) are among all allergic (N=240) and non-allergic (N=298) patients; post-index counts (ie from within the 12-month follow-up period) are among patients with chronic OCS use (≥10 mg/day in the 90 days pre-index); †Measured during the 90 days period prior to the index date; ‡Measured during the 12-month follow-up period among patients with chronic OCS use in the 90 days period prior to the index date.
Abbreviations: CI, confidence interval; DiD, difference-in-difference; OCS, oral corticosteroids.

OCS bursts from baseline to follow-up (DiD RR = 0.954, p = 0.833). The number of patients who were chronic OCS users at baseline in the allergic and non-allergic cohorts decreased by 53.6% and 53.4% at 0–3 months and 80.3% and 83.6% at 10–12 months of follow-up, respectively (Figure 4C). The difference in chronic OCS use between cohorts was significant during months 7–9 (p = 0.044) of the follow-up period but not at any other timepoint.

The proportion of patients with any SABA use, and the mean count of SABA canisters decreased from baseline to follow-up; the change in the proportion of patients with any SABA use was significantly different between cohorts. Change in SABA use from baseline to follow-up is detailed in the Supplementary Figure 2.

Discussion

Real-world evidence on effectiveness of mepolizumab specifically among patients with severe asthma and allergic and non-allergic phenotypes is limited. Although claims datasets are limited by not being designed to address research

questions, this real-world observational cohort study identified clear and consistent beneficial outcomes across the endpoints: mepolizumab treatment significantly reduced asthma exacerbation frequency, and OCS use among patients with allergic and non-allergic phenotypes, with limited differences in outcomes between patient groups. These results suggest that patients with severe asthma in a real-world setting may clinically benefit from mepolizumab treatment irrespective of the presence or absence of an allergic phenotype.

Reductions in asthma exacerbation frequency (~32–34%) in both cohorts were similar magnitudes to those observed in previous real-world retrospective database studies of mepolizumab (34–55%) including those assessing the impact of mepolizumab on patients with life-threatening asthma, with high burden of disease, and with comorbidities.[28,30–34] Similar reductions in exacerbation frequency between cohorts were observed despite patients with allergic versus non-allergic asthma having a significantly higher absolute rate of exacerbations during both the baseline (3.2 vs 2.5 per year) and follow-up periods (2.1 vs 1.7 per year). The higher exacerbation rate in patients with allergic asthma may result from this cohort having more exacerbation triggers than the non-allergic cohort. Some patients could have asthma that is both allergic and non-allergic in nature and that would not have been identified in the dataset and may consequently have impacted the results. Additionally, differences between cohorts in baseline exacerbation levels may have affected this study's ability to assess the overall benefits of therapy. The results of this study contrast with previous post hoc trial analyses (MENSA alone, and MENSA and MUSCA combined), which found similarly high exacerbation rates (3.5–3.8 per year) in non-atopic, atopic, and strongly atopic patients (based on IgE titers to specific allergens) and patients eligible or ineligible for omalizumab (3.2 per year).[16,22] In the OSMO study of patients not optimally controlled with omalizumab, the baseline level of exacerbations was 3.3 per year.[24] Differences in exacerbation rate between the current study and previous clinical trials may arise from the strict eligibility criteria selecting patients in clinical trials resulting in a population of patients with more severe asthma than those in real-world studies. Additionally, this difference may be due to the differing methodology employed in real-world studies: baseline exacerbation rates in previous real-world database studies (2.2–3.2 per year)[28,30–34] were generally lower than in prospective studies (4.3–5.8 per year).[17–20] Nonetheless, our results further support findings suggesting that patients with severe asthma demonstrate reductions in asthma exacerbations irrespective of atopic status, prior omalizumab use, IgE level and sensitivity to particular allergens.[15,16,21–23]

In both cohorts, reductions in OCS use were also observed. Overall OCS use significantly decreased; at baseline, approximately 90% of patients had an OCS claim, during the follow-up period this was reduced to approximately 75% of patients. Daily OCS use was reduced from 5 to 6 mg/day during the baseline period to approximately 3 mg/day during the follow-up period. The reduction in daily OCS use was significantly greater in the non-allergic versus allergic cohort: the former cohort had higher baseline use than the latter cohort (5.6 vs 4.9 mg/day) providing the potential for greater reduction in OCS use in the non-allergic cohort than the allergic cohort, which may confound the observed results. Both cohorts demonstrated 40–45% decreases in OCS burst use, in addition to at least an 80% decrease in the number of patients who were chronic OCS users. Finally, the corticosteroid-sparing effect of mepolizumab appeared to increase over time, with an approximately 50% decrease in the number of chronic users in the first 3 months of mepolizumab initiation and an approximately 80% decrease in the 10–12 months after initiation. Overall, these data align with observations from other real-world studies, which have also demonstrated the corticosteroid sparing effects of mepolizumab among patients with severe asthma.[17–20,27,30,32–34] Results from this study align with those of a retrospective analysis which demonstrated that patients with severe asthma and comorbid atopic disease, nasal polyps and chronic sinusitis all demonstrate similar reductions in OCS use and OCS-dependency with mepolizumab.[28]

Incidence of comorbidities were largely similar at baseline; however, significantly more patients in the allergic asthma cohort reported presence of allergic rhinitis, eosinophilic esophagitis and sinusitis than those in the non-allergic asthma cohort. This is likely because each of these comorbidities were included as an expected or common comorbidity; diagnosis codes for ≥1 expected or common comorbidity was one of the eligibility requirements for the allergic asthma cohort.

This study's findings provide further real-world evidence supporting the clinical targeting of IL-5 and eosinophils in the treatment of severe asthma phenotypes. Blood eosinophil counts are indicative of patients who may benefit from eosinophil-targeting treatment across several biologic therapies with different mechanisms of action.[5,35–37] By contrast, allergen-specific

IgE, a main marker of allergic disease,[3–5] is not predictive of treatment responses, even for anti-IgE therapy with omalizumab.[5] The overlap between allergic and non-allergic phenotypes and the fact that approximately three-quarters of patients with severe asthma with an eosinophilic phenotype also have an allergic phenotype highlights the need to select treatment based on treatable traits.[6,11]

Study limitations to consider when interpreting the results include the inherent limitations of real-world data including potential confounding owing to the lack of a control placebo group, and the retrospective nature of the analysis. In contrast to prospective real-world datasets that can answer research questions robustly, retrospective claims data or electronic health record analyses offer insights into real-world practice, despite their limitations, with reduced time and cost. All patients with an immunotherapy claim were included in the allergic asthma cohort. This may have resulted in some patients with non-allergic asthma being misclassified. To mitigate the risk of misclassification/overlap between allergic/non-allergic asthma, this study used multiple definitions for these conditions that were consistent with clinical knowledge and adaptable to this specific research focus. Claims data may underestimate OCS or other medication use as treatment during hospital admissions are not reported. Finally, more recent data could not be used as the study period was limited to exclude the COVID-19 pandemic, which would likely have been a source of confounding. Most recent medical practice may not be reflected in this study as the study period (2011–2019) included patients who were prescribed mepolizumab shortly after approval in the EU/USA (December 2015)[7,8] who may have been more unwell than patients who would be prescribed mepolizumab in most recent practice.

Conclusions

This study demonstrates the effectiveness of mepolizumab for the treatment of patients with severe asthma with allergic and non-allergic phenotypes, with mepolizumab generally providing similar clinical benefits between phenotypes in terms of less frequent exacerbations and greater reductions in OCS use over time. Together with previous studies, these data suggest a need to target treatable traits such as eosinophils, which can be a common driver of allergic and eosinophilic phenotypes in patients with severe asthma.

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DiD, difference-in-difference; ED, emergency department; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; OCS, oral corticosteroids; ORD, Optum Research Database; RR, rate ratio; SABA, short-acting ß$_2$-agonist; SCS, systemic corticosteroids; SD, standard deviation

Data Sharing Statement

To access data for GSK sponsored research, please submit an enquiry via www.gsk-studyregister.com/en/. Data used to generate these results cannot be disclosed publicly. Proprietary data obtained from Optum may be accessed only with strictest data security and privacy protocols, and oversight with a restrictive license agreement.

Ethics Approval and Informed Consent

This study complied with all applicable laws regarding subject privacy. There was no direct subject contact or primary collection of individual human subject data. Study results omit subject identification; therefore, informed consent, ethics committee or institutional review board approval was not required.

Consent for Publication

Since informed consent was not required for this study, a consent for publication statement is not applicable.

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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

JS and AD are employees of GSK and hold GSK stocks/shares. JS also reports editorial support for manuscript preparation from Fishawack Indica Ltd, part of Avalere Health. AS and BC are employees of Optum, which received funding from GSK to conduct this study.

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