

Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma

Marie-Hélène Lafeuille, MA ^{*}; Jason Dean, PhD ^{*}; Jie Zhang, PhD [†]; Mei Sheng Duh, MPH, ScD [‡]; Boris Gorsh, PharmD [†]; and Patrick Lefebvre, MA ^{*}

^{*} Groupe d'analyse, Ltée, Montréal, Québec, Canada

[†] Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

[‡] Analysis Group, Inc., Boston, Massachusetts

ARTICLE INFO

Article history:

Received for publication February 7, 2012.

Received in revised form April 3, 2012.

Accepted for publication April 20, 2012.

ABSTRACT

Background: Omalizumab is a monoclonal antibody indicated for moderate to severe allergic asthma patients with inadequately controlled symptoms.

Objective: To evaluate the impact of omalizumab on emergency department (ED) visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma using high-dose inhaled corticosteroids (ICS) and long-acting beta₂-agonists (LABA).

Methods: Health insurance claims from the MarketScan database (2002Q1–2009Q1) were analyzed. Patients with 12 months or more of continuous insurance coverage before and after the first omalizumab dispensing, 8 or more weeks of high-dose ICS use, 8 or more weeks of LABA use, and uncontrolled asthma at baseline were included. A retrospective analysis was conducted to quantify the impact of omalizumab on resource use by comparing ED visits, hospitalizations, and corticosteroid use 1 year before and after omalizumab initiation. A 1-year period was chosen to cover any potential seasonality impacts.

Results: In total, 644 patients (mean age, 49.9; female, 59.2%) formed the study population. Omalizumab was associated with a 48.6% reduction in the proportion of patients with 1 or more asthma-related ED visits (pre vs post-omalizumab period: 21.4% vs 11.0%; $P < .001$) and a 40.8% reduction in asthma-related hospitalizations (25.0% vs 14.8%, respectively, $P < .001$). Compared with the pre-omalizumab period, the use of ICS decreased significantly after omalizumab initiation (7.8 vs 6.5 dispensings, $P < .001$; 41.9% of patients had a reduction in ICS use). A similar reduction in oral corticosteroid use was observed (5.0 vs 3.6 dispensings, $P < .001$; 53.3% of patients had a reduction in oral corticosteroid use).

Conclusion: The current analysis showed that omalizumab treatment initiation was associated with significant reductions in ED visits, hospitalizations, and corticosteroid use.

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Introduction

Asthma is a chronic inflammatory disease of the airways characterized by shortness of breath, coughing, wheezing, and chest tightness.^{1,2} In 2009, asthma prevalence was 8.2%, affecting approximately 17.5 million adults and 7.1 million children.^{3,4} Among patients with current asthma, the proportion of patients with asthma attacks and at risk for adverse outcomes such as emergency-department (ED) visits or hospitalizations in one year was 52%.⁵ In

2007, asthma accounted for 13.9 million physician office visits, 456,000 hospitalizations, and 1.8 million ED visits.⁵

The goal of asthma pharmacologic therapy is to achieve control, defined as limiting the current impairment and reducing the risk for future deterioration and exacerbations.⁶ The 2007 National Asthma Education and Prevention Program (NAEPP) recommends a stepwise approach for managing asthma.² Treating the mildest, intermittent form of asthma with short-acting beta₂-agonists (SABA) is recommended, whereas inhaled corticosteroids (ICS) are usually prescribed for all other types of asthma, with increasing dosage with disease severity. In moderate to severe cases, the suggested therapies include high-dose ICS and long-acting beta₂-agonists (LABA) (step 5) or high-dose ICS, LABA, and oral corticosteroids (step 6).²

Among patients receiving a regimen of high-dose ICS and LABA, roughly one third are still not able to adequately control their asthma symptoms.⁷ Leukotriene receptor antagonists and oral cor-

Reprints: Patrick Lefebvre, Vice President, Groupe d'analyse, Ltée 1000 De La Gauchetière West, Suite 1200, Montréal, QC H3B 4W5; E-mail: plefebvre@analysisgroup.com.

Disclosures: Drs. Lafeuille, Dean, Duh, and Lefebvre are employees of Analysis Group, Inc., a consulting company that has received research grants from Novartis Pharmaceuticals Corporation. Zhang and Gorsh are employees of Novartis Pharmaceuticals Corporation.

Funding Sources: This study was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ.

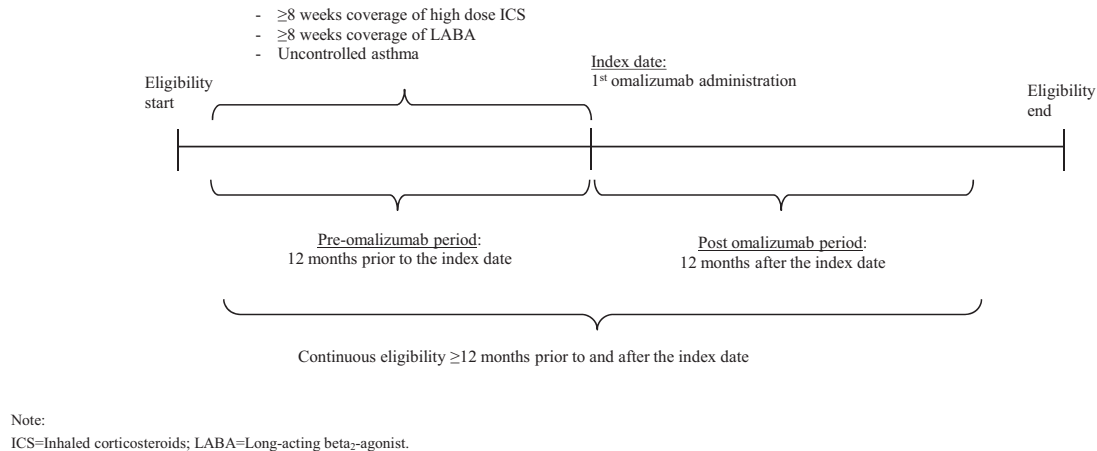


Fig. 1. Study design scheme.

ticosteroids (OCS) are options for further adjunctive therapy, but concerns exist related to their safety and effectiveness.^{2,8–11}

Omalizumab, a recombinant humanized anti-immunoglobulin E, is currently approved by the US FDA for the treatment of adults and adolescents (aged 12 years or older) with moderate to severe persistent allergic asthma that is inadequately controlled with ICS.¹² According to the NAEPP guidelines, omalizumab may be considered in moderate to severe asthma and allergies (ie, steps 5–6).² Most of the previously published randomized, double-blind, placebo-controlled trials have studied omalizumab as an adjunctive therapy to high-dose ICS.^{13–16} Since the publication of the omalizumab pivotal trials, the standard of care has evolved to include high-dose ICS and LABA.² More recently, 2 multicenter, randomized, double-blind, placebo-controlled trials and 1 open-label study analyzed the efficacy, safety, and tolerability of subcutaneously administered omalizumab as add-on therapy to high-dose ICS and LABA.^{17–19} However, to the authors' knowledge, no study has yet evaluated the effectiveness of omalizumab in combination with high-dose ICS and LABA in a real-world setting. The current study aims to evaluate the impact of omalizumab on ED visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma who are using high-dose ICS and LABA.

Methods

Data source

The MedStat MarketScan database is a large, fully Health Insurance Portability and Accountability Act–compliant, integrated, de-identified, individual-level database containing data from approximately 45 large employers, health plans, and government and public organizations and covering over 18 million lives. Enrollees in the database include employees, dependents, and retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans, from all US census regions. The data used in the current analysis covered the period from January 2002 through March 2009 and includes the Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases. Institutional review board was not required for this study.

Study design and population

A retrospective pre–post cohort study design was chosen for this study. To be included in the study population, patients were required to have at least 1 pharmacy (National Drug Codes: 50242004062; 50242004201) or medical (Healthcare Common Procedure Coding System: J2357; S0107; C9217) dispensing of

omalizumab and at least 12 months of continuous insurance coverage before and after the first omalizumab dispensing, termed as the study index date. In addition, patients were required to have uncontrolled asthma (see definition below) with at least 8 weeks of coverage for high-dose ICS and LABA during the 12-month baseline period.¹⁹ The post-omalizumab period was defined as the 12 months after omalizumab initiation, whereas the pre-omalizumab period was defined as the 12 months preceding omalizumab initiation. Figure 1 summarizes the study design scheme.

Identification of high-dose ICS

To identify patients receiving high-dose ICS, daily doses of ICS were calculated based on the following formula: (strength per puff [in micrograms] × number of puffs per canister × number of canisters) / number of days of supply. High-dose thresholds were identified based on the estimated comparative daily dosages recommended by the NAEPP EPR-3 guidelines for patients 12 years of age or older (beclomethasone hydrofluoroalkane (HFA): >1,280 µg; budesonide dry powder inhaler (DPI): >1,600 µg; flutisolid metered dose inhaler (MDI): >2,000 µg; fluticasone hydrofluoroalkane/MDI: >880 µg; fluticasone DPI: >1,000 µg; mometasone DPI: >880 µg).⁵

Identification of patients with uncontrolled asthma

The identification of uncontrolled asthma was based on patients meeting either impairment or risk criteria in a 1-year consecutive period.²⁰ Impairment was identified as 7 or more SABA prescriptions dispensed in 1 year. Risk was defined as 2 or more unique exacerbations, including asthma-related emergency department visits or hospitalizations (emergency or hospital care with a diagnosis of asthma [ICD-9 code 493.xx]) or oral corticosteroid pharmacy claims with a provider visit for asthma within 2 days of dispensing. The date of uncontrolled asthma assessment was defined as the earliest date between the seventh SABA prescription or the second exacerbation event during a consecutive 1-year interval. If the uncontrolled asthma identification occurred before the 12-month pre-omalizumab period, patients were still considered uncontrolled if they had 2 or more SABA prescriptions, 1 or more asthma-related emergency department visits or hospitalizations, or 1 or more OCS prescriptions within 2 days after an asthma-related physician visit during the pre-omalizumab baseline period.

Statistical analysis

Patients' baseline demographic and clinical characteristics, including age, sex, geographical region, season and year of index date,

baseline asthma medication use, Quan-Charlson comorbidity index,²¹ and relevant comorbidities (extrinsic asthma, allergic rhinitis, respiratory infections, chronic sinusitis, acute sinusitis, chronic obstructive pulmonary disease) were reported.

The following statistical analyses were preplanned to assess the impact of omalizumab initiation on asthma control and corticosteroid use. Asthma control was evaluated by assessing the frequency of patients experiencing at least 1 ED visit, at least 1 hospitalization, and the mean number of ED visits and hospitalizations. All-cause events as well as asthma-related events (events associated with a diagnosis of asthma) were reported separately. In addition, corticosteroid use was assessed by evaluating the number of dispensings, the number of non-overlapping days with supply, and the proportion of days covered (PDC), defined as the sum of non-overlapping days of supply divided by the number of days in the period, of any ICS and OCS compounds. Finally, the proportion of patients experiencing a reduction in use of either medication after omalizumab initiation, defined as patients with a decrease in the cumulative dose of an ICS or OCS compound and in the total cumulative dose of ICS and OCS compounds post- versus pre-omalizumab period, was evaluated. These analyses were performed additionally in a pre-specified subpopulation of patients who received OCS (defined as OCS within 2 days of an asthma-related physician visit) during the baseline period.

The impact of omalizumab persistence on corticosteroid use was assessed as a prespecified exploratory analysis. Persistent patients were identified as the subgroup of patients with no gap of more than 45 days between the end of an omalizumab prescription and the subsequent dispensing, assuming 28 days of supply for medical claims. The remaining patients for whom a gap of 45 days was observed during omalizumab treatment were defined as non-persistent.

Differences in the aforementioned outcomes between the pre- and post-omalizumab periods were calculated to evaluate the impact of omalizumab initiation on asthma control. A 1-year period was chosen to cover any potential seasonality impact in the pre- and post-periods. Descriptive statistics included the mean ($\pm$ standard deviation [SD]) and median values for continuous data and relative frequencies for categorical data. Statistical tests comparing the pre- and the post-omalizumab periods were performed using McNemar tests for categorical variables and 2-sided paired Student's *t* tests for continuous variables. Statistical significance was assessed with a 2-sided test at α -level of 0.05 or less. All statistical analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline demographics and clinical characteristics

Baseline demographics are shown in Table 1. A total of 644 patients were identified. Mean (median) age was 49.9 (53.0), and 95.2% of patients were older than 18 years of age. A total of 59.2% of patients were female. Initiation of omalizumab occurred more predominantly in the spring (29.8%), followed by the winter (25.3%), and less frequently in the summer (22.5%) or the fall (22.4%).

Table 1 displays the baseline clinical characteristics of the study population. In addition to their prescriptions for LABA and ICS, most patients also had at least 1 prescription for SABA (95.3%), OCS (93.5%), and leukotriene modifiers (87.4%). Patients scarcely used methylxanthines (0.5%) and mast cell stabilizers (5.6%). Anticholinergics were used by 38.0% of patients.

Impact of omalizumab on ED visits and hospitalizations

Emergency department visits and hospitalizations during the pre- and post-omalizumab periods are reported in Table 2. Omalizumab was associated with a 29.4% reduction in the proportion of

Table 1

Baseline demographic and clinical characteristics

	Omalizumab patients N = 644
Age at index date, mean $\pm$ SD [median]	49.9 $\pm$ 14.2 [53.0]
Age categories, N (%)	
<12 years old	8 (1.2%)
12–17 years	23 (3.6%)
$\geq$ 18 years	613 (95.2%)
Female, N (%)	381 (59.2%)
Region, N (%)	
North central	190 (29.5%)
Northeast	67 (10.4%)
South	264 (41.0%)
West	121 (18.8%)
Unknown	2 (0.3%)
Season of index date, N (%)	
Winter (Dec 22–Mar 19)	163 (25.3%)
Spring (Mar 20–June 20)	192 (29.8%)
Summer (June 21–Sept 22)	145 (22.5%)
Fall (Sept 23–Dec 21)	144 (22.4%)
Year of index date, N (%)	
2003	41 (6.4%)
2004	105 (16.3%)
2005	173 (26.9%)
2006	127 (19.7%)
2007	143 (22.2%)
2008	55 (8.5%)
Baseline asthma medication N (%)	
LABA	644 (100.0%)
Number of claims, mean $\pm$ SD [median]	5.1 $\pm$ 3.1 [4.0]
SABA	614 (95.3%)
Number of claims, mean $\pm$ SD [median]	7.4 $\pm$ 6.0 [6.0]
ICS	644 (100.0%)
Number of claims, mean $\pm$ SD [median]	7.8 $\pm$ 5.6 [6.0]
OCS	602 (93.5%)
Number of claims, mean $\pm$ SD [median]	5.0 $\pm$ 3.7 [4.0]
Leukotriene modifiers	563 (87.4%)
Number of claims, mean $\pm$ SD [median]	4.7 $\pm$ 3.7 [4.0]
Methylxanthines	3 (0.5%)
Number of claims, mean $\pm$ SD [median]	0.0 $\pm$ 0.2 [0.0]
Mast cell stabilizers	36 (5.6%)
Number of claims, mean $\pm$ SD [median]	0.2 $\pm$ 1.6 [0.0]
Anticholinergics	245 (38.0%)
Number of claims, Mean $\pm$ SD [median]	1.5 $\pm$ 3.1 [0.0]
Quan-Charlson comorbidity index, mean $\pm$ SD [median]	0.4 $\pm$ 0.8 [0.0]
Comorbidities, N (%)	
Extrinsic asthma	415 (64.4%)
Allergic rhinitis	348 (54.0%)
Respiratory infections	327 (50.8%)
Chronic sinusitis	223 (34.6%)
Acute sinusitis	163 (25.3%)
Chronic obstructive pulmonary disease	116 (18.0%)

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta₂-agonist; OCS, oral corticosteroids; SABA, short-acting beta₂-agonist.

patients with all-cause ED visits (pre- vs post-omalizumab period: 39.1% vs 27.6%, $P < .0001$) and a 28.1% reduction in all-cause hospitalizations (30.6% vs. 22.0%, respectively, $P < .0001$). Reductions in the mean number of these events were also observed (pre- vs post-omalizumab period: ED visits: 0.81 vs 0.55 [32.1% of reduction; $P < .0001$]; hospitalizations: 0.48 vs 0.33 [31.3% of reduction; $P < .0001$]). The reduction in resource use was more pronounced when considering asthma-related events, where omalizumab was associated with a 48.6% (21.4% vs 11.0%, $P < .001$) reduction in the proportion of patients with ED visits and a 40.8% (25.0% vs 14.8%, $P < .001$) reduction in hospitalizations. Reductions in the mean number of asthma-related events were also more pronounced, with reductions of 42.9% (0.35 vs 0.20; $P = .0002$) and 41.7% (0.36 vs 0.21; $P = .0002$) in ED visits and hospitalizations, respectively. These results were consistent in the subpopulation of patients using OCS at baseline, defined as those with a dispensing for OCS

Table 2
ED visits and hospitalizations during pre- and post-omalizumab periods

	Pre-omalizumab [A]	Post-omalizumab [B]	% Reduction ([B] - [A])/[A]	P-value
All omalizumab patients (N = 644)				
All-cause events				
Patients with ≥ 1 ED visits, N (%)	252 (39.1%)	178 (27.6%)	-29.4%	<.0001
Number of ED visits, mean $\pm$ SD [median]	0.81 $\pm$ 1.59 [0]	0.55 $\pm$ 1.31 [0]	-32.1%	<.0001
Patients with ≥ 1 hospitalization, N (%)	197 (30.6%)	142 (22.0%)	-28.1%	<.0001
Number of hospitalizations, mean $\pm$ SD [median]	0.48 $\pm$ 0.92 [0]	0.33 $\pm$ 0.79 [0]	-31.3%	.0001
Days in hospital, mean $\pm$ SD [median]	2.41 $\pm$ 5.10 [0]	2.13 $\pm$ 6.48 [0]	-11.6%	.2922
Asthma-related events ^a				
Patients with ≥ 1 ED visits, N (%)	138 (21.4%)	71 (11.0%)	-48.6%	<.0001
Number of ED visits, mean $\pm$ SD [median]	0.35 $\pm$ 0.96 [0]	0.20 $\pm$ 0.72 [0]	-42.9%	.0002
Patients with ≥ 1 hospitalization, N (%)	161 (25.0%)	95 (14.8%)	-40.8%	<.0001
Number of hospitalizations, mean $\pm$ SD [median]	0.36 $\pm$ 0.77 [0]	0.21 $\pm$ 0.59 [0]	-41.7%	<.0001
Days in hospital, mean $\pm$ SD [median]	1.83 $\pm$ 4.28 [0]	1.42 $\pm$ 5.49 [0]	-22.4%	.0653
Subgroup of patients using high-dose ICS, LABA, and OCS at baseline (N = 439)				
All-cause events				
Patients with ≥ 1 ED visits, N (%)	187 (42.6%)	124 (28.2%)	-33.8%	<.0001
Number of ED visits, mean $\pm$ SD [median]	0.87 $\pm$ 1.69 [0]	0.58 $\pm$ 1.36 [0]	-33.3%	.0006
Patients with ≥ 1 hospitalization, N (%)	132 (30.1%)	96 (21.9%)	-27.3%	.0015
Number of hospitalizations, mean $\pm$ SD [median]	0.49 $\pm$ 0.96 [0]	0.31 $\pm$ 0.69 [0]	-36.7%	.0002
Days in hospital, mean $\pm$ SD [median]	2.42 $\pm$ 5.16 [0]	1.88 $\pm$ 5.69 [0]	-22.3%	.0957
Asthma-related events ^a				
Patients with ≥ 1 ED visits, N (%)	106 (24.1%)	52 (11.8%)	-51.0%	<.0001
Number of ED visits, mean $\pm$ SD [median]	0.42 $\pm$ 1.09 [0]	0.21 $\pm$ 0.70 [0]	-50.0%	.0001
Patients with ≥ 1 hospitalization, N (%)	116 (26.4%)	65 (14.8%)	-43.9%	<.0001
Number of hospitalizations, mean $\pm$ SD [median]	0.39 $\pm$ 0.80 [0]	0.21 $\pm$ 0.57 [0]	-46.2%	<.0001
Days in hospital, mean $\pm$ SD [median]	1.91 $\pm$ 4.17 [0]	1.30 $\pm$ 4.98 [0]	-31.9%	.0214

Abbreviations: ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting beta₂-agonist; OCS, oral corticosteroids.^aAsthma-related events were identified as the subset of events with a primary or secondary diagnosis of asthma (ICD-9 diagnosis: 493.xx).

within 2 days of an asthma-related physician visit during the pre-omalizumab period (Table 2).

Impact of omalizumab on corticosteroid use

Table 3 presents results on corticosteroid use for the pre- and post-omalizumab periods. Compared with the pre-omalizumab period, the use of ICS decreased significantly after omalizumab initiation (7.8 vs 6.5 dispensings, $P < .0001$; 41.9% of patients had a reduction in ICS use). A similar reduction in OCS use was observed (5.0 vs 3.6 dispensings, $P < .0001$; 53.3% of patients had a reduction in oral corticosteroid use). When stratified by omalizumab persistence, patients persistent to omalizumab experienced a higher reduction in terms of OCS use (Fig. 2). The reduction in the number

of OCS prescriptions, in PDC, and the reduction in use was 35.8%, 15.7%, and 57.1% for persistent patients, compared with 19.1%, 10.0%, and 48.6% for nonpersistent patients, respectively. The reduction of ICS use was similar between persistent and nonpersistent patients.

Discussion

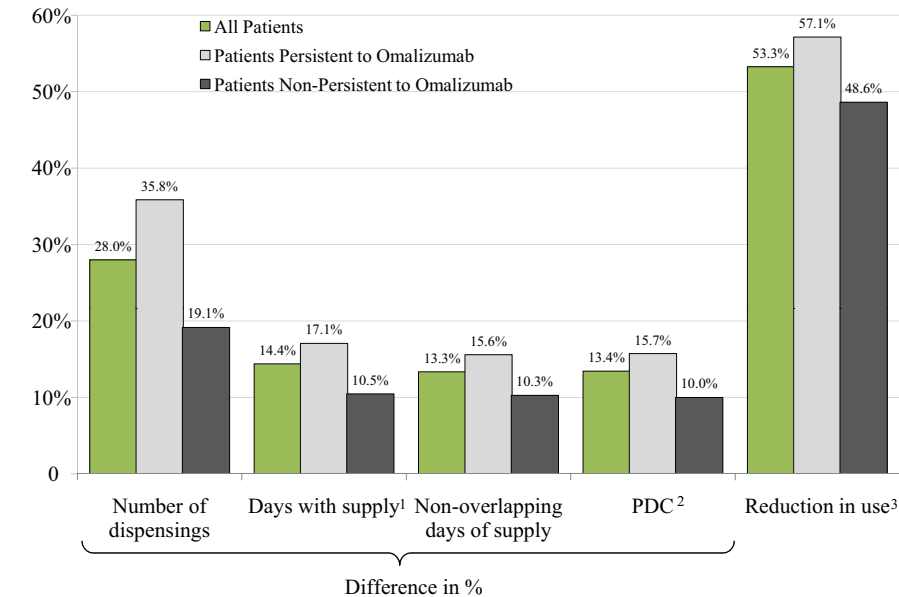
This study examined the impact of omalizumab treatment on ED visits, hospitalizations, and corticosteroid use in patients with asthma with inadequately controlled symptoms using high-dose ICS and LABA. In this study, a total of 644 patients with uncontrolled asthma, who initiated omalizumab and were taking high-dose ICS and LABA, were identified from a large medical claims database. A

Table 3
Corticosteroid use during pre- versus post-omalizumab periods

	Omalizumab patients			
	N = 644			
	Pre-omalizumab [A]	Post-omalizumab [B]	% Reduction ([B] - [A]) / [A]	P-value
ICS				
Number of dispensings, mean $\pm$ SD [median]	7.8 $\pm$ 5.6 [6.0]	6.5 $\pm$ 5.7 [5.0]	-16.7%	<.0001
Days of supply, ^a mean $\pm$ SD [median]	334.1 $\pm$ 213.7 [285.0]	296.0 $\pm$ 223.8 [270.0]	-11.4%	<.0001
Non-overlapping days of supply, mean $\pm$ SD [median]	226.2 $\pm$ 93.5 [229.0]	205.6 $\pm$ 112.0 [218.0]	-9.1%	<.0001
PDC (%), ^b mean $\pm$ SD [median]	62.0% $\pm$ 25.6 [62.7]	56.3% $\pm$ 30.7 [59.7]	-9.2%	<.0001
Patients with a reduction in ICS use, ^c N (%)		270 (41.9%)		
OCS				
Number of dispensings, mean $\pm$ SD [median]	5.0 $\pm$ 3.7 [4.0]	3.6 $\pm$ 4.0 [2.0]	-28.0%	<.0001
Days of supply, ^a mean $\pm$ SD [median]	91.0 $\pm$ 101.5 [55.0]	77.9 $\pm$ 114.5 [30.0]	-14.4%	.0002
Nonoverlapping days of supply, mean $\pm$ SD [median]	78.7 $\pm$ 78.2 [50.0]	68.2 $\pm$ 85.8 [33.0]	-13.3%	<.0001
PDC (%), ^b mean $\pm$ SD [median]	21.6% $\pm$ 21.4 [13.7]	18.7% $\pm$ 23.5 [9.0]	-13.4%	<.0001
Patients with a reduction in OCS use, ^c N (%)		343 (53.3%)		

Abbreviations: ICS, Inhaled corticosteroids; OCS, Oral corticosteroids; PDC, proportion of days covered.

^aCalculated as the sum of the days of supply of the prescription claims within each period.^bCalculated as the number of nonoverlapping days' supply divided by the number of days in the pre- or post-omalizumab period (365 days).^cDefined as patients with a decrease in the cumulative dose of an ICS or OCS compound and in the total cumulative dose of ICS and OCS compounds post- versus pre-omalizumab period.

**Notes:**

OCS = Oral corticosteroids; PDC = Proportion of days covered.

1. Calculated as the sum of the days of supply of the prescription claims within each period.

2. Calculated as the number of non-overlapping days of supply divided by the number of days in the pre- or post-omalizumab period (365 days).

3. Defined as patients with a decrease in the cumulative dose of an ICS or OCS compound and in the total cumulative dose of ICS and OCS compounds post- versus pre-omalizumab period.

Fig. 2. Reduction in OCS use for patients persistent vs nonpersistent to omalizumab.

comparison of pre- and post-omalizumab outcomes demonstrated that omalizumab was associated with a 48.6% reduction in ED visits and a 40.8% reduction in hospitalizations. Moreover, the proportion of patients who reduced their ICS and OCS use was 41.9% and 53.3%, respectively. Reductions in OCS were greater for the subgroup of patients persistent to omalizumab.

Initial pivotal trials of omalizumab have documented its beneficial impact on the number of asthma exacerbations and improved patients' quality of life.^{13–16} However, these studies did not include patients using LABA as an adjunctive therapy to high-dose ICS. More recent clinical studies have assessed the safety and efficacy of omalizumab in adjunction to high-dose ICS and LABA.^{17–19} To the authors' knowledge, the current study is the first to show that omalizumab is an effective add-on option for patients with severe asthma classified into steps 5 and 6 of the NAEPP guidelines using real-world data. Although Hanania et al¹⁹ could not find a statistical difference in the subpopulation of patients also using OCS at baseline, the results from this study suggest that omalizumab is also effective in this subpopulation.¹⁹ Two clinical studies have reported differences in ED visits and hospitalizations between omalizumab and control groups.^{17,18} One of these studies found a statistically significant difference in asthma-related ED-visits, with a rate of ED visits of 0.24 for omalizumab patients compared with 0.43 for control patients ($P = .038$).¹⁷ The current study shows that omalizumab has a significant impact not only on the reduction of asthma-related ED visits but also on hospitalizations. The impact of omalizumab on medical resource use is an important consideration, because it is directly related to the cost burden imposed on the health care system. In addition to direct health care costs, quality of life, productivity, and other indirect measures would need to be considered to accurately account for the cost burden of omalizumab.

Furthermore, many studies have reported that omalizumab reduces ICS and OCS use.^{13–15,18,22} The current study corroborates these findings, with a reduction in the use of ICS observed for 41.9% of the patients. The current study has also found that 53.3% of patients have reduced their utilization of OCS. A reduction in OCS was observed regardless of the metric analyzed, suggesting that the reduction occurred for patients using various OCS regimens. The

reduction in OCS use was even greater for patients persistent to omalizumab during the first year after initiation. The adverse effects of OCS are widely known and include fractures and gastric conditions.^{11,23} Adverse effects are strongly correlated with the total cumulative dose of OCS taken. Of note, the definition of OCS use at baseline (≥ 1 dispensing for OCS within 2 days of an asthma-related physician visit) did not allow determination of whether the patients were steroid dependent.

This analysis used a pre-post design in which each subject acted as his or her own control. In observational studies, this approach avoids the need to identify a comparable control group, thus avoiding the risk of confounding by indication, the need to control for potential selection biases, and the problems associated with unobserved and uncontrollable confounders.²³ However, the pre-post approach implies that the observed differences in the outcomes pre- and post-omalizumab initiation were only attributable to the addition of omalizumab. For instance, it assumes no period or time effects and that pre-omalizumab resource/corticosteroid use does not influence resource/corticosteroid use in the post-omalizumab period.^{24,25} To mitigate this potential issue, a relatively short period, 1 year, before and after omalizumab treatment for comparisons was chosen. In addition, the pre-post design of this study assumes that the decrease in ICS use observed during the post-omalizumab period is attributable to omalizumab and not to a change in ICS/LABA compliance that could also influence ED visits and hospitalizations. However, this is a conservative assumption, because a reduction in ICS attributable to reduced compliance would likely increase the risk of ED visits and hospitalizations.

The present study is subject to other limitations that are inherent in the analysis of administrative claims databases. First, claims data may be subject to inaccuracies in billing information and missing data. Also, pharmacy dispensing claims may not reflect patients' actual compliance to the medications. In addition, claims data do not include certain information such as reasons for treatment or disease severity, which would be available from a clinical trial. For example, the fact that only 64% of patients had a diagnosis for extrinsic asthma during the baseline period, even if omalizumab is indicated for patients with allergic asthma, may be explained by some patients having had an extrinsic asthma diagnosis during a

period other than the baseline period, or physicians using a more general code while recording the claim (eg, 493) and not specifying the type of asthma. However, health insurance claims data allow treatment patterns to be examined in a real-world setting that is free of intervention bias and potentially more representative of the study population.

This real-world study using a health insurance claims database showed that omalizumab has beneficial impacts on ED visits, hospitalizations, and corticosteroid use in patients with uncontrolled asthma using high-dose ICS and LABA. Omalizumab was shown to be associated with a 48.6% reduction in the proportion of patients with 1 or more asthma-related ED visits and a 40.8% reduction in asthma-related hospitalizations. Moreover, both inhaled and oral corticosteroid use decreased significantly after omalizumab initiation. These results corroborate the findings from clinical trials showing that omalizumab is an effective adjunctive therapy option for patients with uncontrolled asthma using high-dose ICS and LABA.

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