

Association Between Consistent Omalizumab Treatment and Asthma Control

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What is already known about this topic? Omalizumab is approved by the US Food and Drug Administration for the treatment of adults and adolescents (aged ≥ 12 years) with moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids and has been shown to be effective in patients receiving high-dose inhaled corticosteroids plus long-acting β_2 -agonists.

What does this article add to our knowledge? This study found that, among responders to omalizumab, consistent administration of omalizumab at recommended dosing intervals for 12 months (39% of patients) is associated with greater overall asthma control with significant reductions in emergency department visits and hospitalizations (reduction of 51% and 28%, respectively).

How does this study impact current management guidelines? The less-than-ideal rate of consistent omalizumab treatment found in this study suggests that physicians should strive for optimal adherence with omalizumab to improve the effectiveness of this treatment regimen.

BACKGROUND: Omalizumab is indicated for patients with moderate-to-severe allergic asthma with inadequately controlled symptoms.

OBJECTIVE: We evaluated the association between consistent omalizumab treatment and asthma control.

METHODS: Health insurance claims from the MarketScan database (2002Q1-2011Q2) were analyzed. Asthmatic patients with ≥ 12 months of continuous insurance coverage after the first omalizumab claim (index date) after 6 months of continuous omalizumab use were included. A 12-month landmark period was used to assess treatment consistency, defined as uninterrupted treatment without a gap of ≥ 28 days in omalizumab use. The effect of consistent omalizumab treatment on asthma control between months 13 and 24 was evaluated. Multivariate time-varying Cox regressions were also conducted to assess the adjusted effect of treatment interruption on asthma control from month 1 to month 24.

RESULTS: A total of 3044 patients (mean age, 48.5 years; female, 62%) formed the study population. Patients consistent

with omalizumab treatment at 12 months (39% of patients) were less likely to have an uncontrolled asthma event during months 13 to 24 with only 49% of patients experiencing one event compared with 54% in the nonconsistent subgroup ($P = .02$). In addition, consistent omalizumab treatment at 12 months was associated with a 51% reduction in the mean number of asthma-related emergency department (ED) visits per patient and a 28% reduction in asthma-related hospitalizations. Multivariate analyses corroborated these findings (hazard ratio for consistent vs non-consistent: risk of short-acting β_2 -agonists prescription, oral corticosteroids prescription, ED visit, or hospitalization, 0.76; 95% CI, 0.69-0.83)).

CONCLUSION: This analysis showed that consistent omalizumab treatment was associated with significant reductions in ED visits and hospitalizations. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:51-7)

Key words: Omalizumab; Asthma treatment; Adherence; Persistence; Asthma control; Resource utilization; Hospitalizations; Emergency department visits; Claims data

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Asthma affects an estimated 300 million people worldwide among both sexes and across all ethnic groups.¹ In the United States, because the number of asthma cases has more than doubled since 1980 and >5500 persons die of asthma-related causes each year, asthma has emerged as a major public health problem.² In 2007, asthma accounted for approximately 13.9 million physician office visits, 456,000 hospitalizations, and 1.8 million emergency department (ED) visits.³

Asthma severity is broad, ranging from mild with occasional symptoms to severe with frequent and potentially fatal exacerbations of the disease.³ A combination of both quick relief and long-term medication is generally effective to achieve asthma control.⁴ Most patients respond to treatment with inhaled corticosteroids (ICSs) alone or with the addition of long-acting β_2 -agonists (LABAs).⁵ In moderate-to-severe cases, the therapies suggested by

Abbreviations used

ED- Emergency department

HR- Hazard ratio

IDC-9- International Classification of Diseases, Ninth Revision

ICS- Inhaled corticosteroids

LABA- Long-acting β_2 -agonists

OCS- Oral corticosteroids

PDC- Proportion of days covered

SABA- Short-acting β_2 -agonists

the guidelines of the National Asthma Education and Prevention Program include high-dose ICSs and LABAs (step 5) or high-dose ICSs, LABAs, and oral corticosteroids (OCSs) (step 6).⁶ For patients with allergic asthma, omalizumab, a recombinant, humanized anti-IgE antibody administered subcutaneously, may be considered as an adjunctive therapy.⁶ Omalizumab is approved by the US Food and Drug Administration for the treatment of adults and adolescents (aged ≥ 12 years) with moderate-to-severe persistent allergic asthma that is inadequately controlled with ICSs⁷ and has been shown to be effective in patients receiving high-dose ICSs plus LABAs.⁸

Poor adherence to ICS controller medication may be an important contributor to uncontrolled asthma, which can affect quality of life because it is associated with increased risk of morbidity and health care costs.⁹⁻¹² Patients with advanced forms of the disease or difficult-to-control asthma appear to be less compliant than patients with mild or moderate forms of the disease.^{11,13-15} In addition to their unique mechanisms of action, injected medications for the treatment of asthma, such as omalizumab, may have adherence benefits that could improve disease control for asthmatic patients.¹⁵

The present study aimed to evaluate the effect of consistent omalizumab treatment on asthma control among responders to omalizumab in a real-world setting with the use of a health administrative claims database.

METHODS**Data source**

The MedStat MarketScan database is a de-identified, individual-level database fully compliant with the Health Insurance Portability and Accountability Act, containing data from approximately 45 large employers, health plans, and government and public organizations and covering >18 million people. 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. All census regions are represented, predominantly the South and North Central (Midwest) regions. The data used in the present analysis covered the period from January 2002 through June 2011 and included inpatient, outpatient, pharmacy, and enrollment information for the Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits databases. Institutional review board and informed consent were not required for this study.

Study design and patient selection

A retrospective cohort study design was used to assess consistency of treatment with omalizumab and to evaluate the effect of consistent omalizumab treatment on asthma control. Patients (aged ≥ 12 years) included in the study had ≥ 1 dispensing of omalizumab

(National Drug Codes: 50242004062, 50242004201; Healthcare Common Procedure Coding System codes: J2357, S0107, C9217), had ≥ 6 months of continuous eligibility before their first omalizumab dispensing (washout period), and had ≥ 1 diagnosis for asthma (International Classification of Diseases, Ninth Revision [ICD-9], 493.x) during the baseline period. As a proxy to identify responders to omalizumab, the study index date was defined as the first omalizumab dispensing after 6 months of continuous omalizumab use (≥ 4 claims during the baseline period). Patients also had to have ≥ 12 months of continuous eligibility after the index date (landmark period for treatment consistency assessment). The follow-up period to evaluate asthma control was defined as the 12 months after the landmark period. Figure 1 summarizes the study design scheme.

Outcomes and statistical analysis

Baseline characteristics. Patients' baseline demographic and clinical characteristics, including age, sex, region, and year of index date, as well as baseline use of asthma medication, asthma-related comorbidities, and the Charlson Comorbidity Index,^{16,17} were evaluated. All-cause and asthma-related baseline resource utilization as well as pharmacy claims for LABAs, short-acting beta₂-agonists (SABAs), ICSs, OCSs, leukotriene modifiers, methylxanthines, mast cell stabilizers, anticholinergics, monoclonal antibodies, and fixed-dose combinations were also analyzed. Means $\pm$ SDs and median values were reported for continuous data and relative frequencies for categorical data.

Adherence and consistency. Patients' adherence to omalizumab was assessed with proportion of days covered (PDC), defined as the sum of unique days of supply of omalizumab divided by the total number of days. Similar to Broder et al,¹⁵ a 28-day supply was assumed for omalizumab medical and pharmacy claims with missing information. As commonly defined, patients with a PDC $\geq 80\%$ were categorized in the adherent subgroup, whereas patients with a PDC $<80\%$ were considered as nonadherent to treatment.^{18,19} Consistent patients at month 12 and month 24 were identified as the subgroup of patients with no gap ≥ 28 days between the end of an omalizumab dispensing (dispensing date plus days of supply) and the subsequent dispensing during these periods. The remaining patients for whom a gap of 28 days was observed were defined as nonconsistent.

Asthma control. Patients with asthma control were identified as patients who did not have an uncontrolled asthma event, defined as ≥ 1 ED visit or hospitalization associated with a diagnosis of asthma (ICD-9 code, 493.x), ≥ 6 pharmacy claims for SABAs, or ≥ 2 OCS pharmacy claims during a 12-month period.¹⁵ The uncontrolled asthma date was defined as the earliest date between the first of an asthma-related ED visit or hospitalization, the sixth pharmacy claim for SABAs, or the second OCS claim.

Landmark analyses. To evaluate the effect of consistent omalizumab treatment on asthma control, the asthma control end points defined in "Asthma control" were evaluated during the follow-up period (months 13-24) and compared between consistent and nonconsistent patients during the landmark period. As a subgroup analysis, the patients consistent at 12 months that remained consistent at 24 months were compared with the patients who were not consistent at 12 months and never reinitiated omalizumab during the 24 months. Statistical differences between

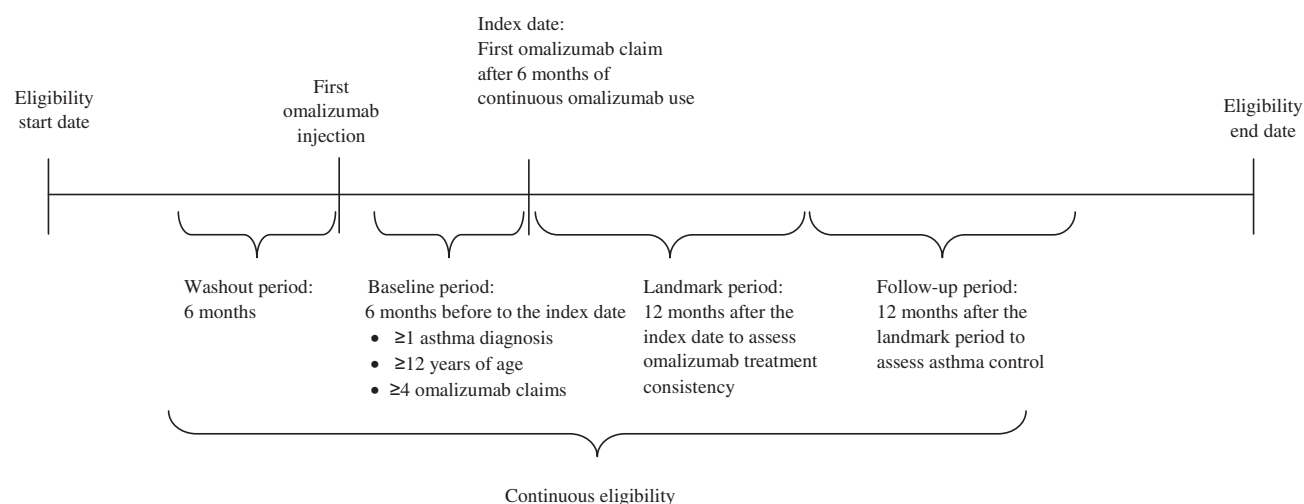


FIGURE 1. Study design scheme.

the subgroups were calculated with Pearson χ^2 tests for categorical variables and Student t tests for continuous variables. As a sensitivity analysis, the effect of consistent omalizumab treatment on uncontrolled asthma was also assessed with a multivariate logistic regression that controlled for baseline characteristics.

Time-varying Cox regressions. Multivariate analyses with Cox regression models were conducted to evaluate the effect of omalizumab treatment on asthma control with the use of a time-varying omalizumab treatment status variable during the 24-month study period. The omalizumab treatment status variable was created on the basis of the date of failure of treatment consistency, which was the end of the days of supply of the last dispensing before a gap of ≥ 28 days. Omalizumab consistency status was set as 1 for the time period before this date and 0 afterward. Patients were censored at the earliest date between loss of eligibility and 24 months. In the first model, the dependent variable was the time to uncontrolled asthma, defined as the time to the first event among the following: first asthma-related ED visit or hospitalization, sixth SABA claim, or second OCS claim. As a sensitivity analysis, the dependent variable of the second model was restricted to the time to first asthma-related ED visit or hospitalization, the most severe outcomes. Covariates used in the models included age, sex, region, year of index date, Charlson Comorbidity Index, baseline asthma medication use, baseline asthma-related comorbidities, and baseline asthma-related resource utilization. Hazard ratios (HRs) with 95% CIs and P values were calculated for time-varying consistency status and covariates. As a subgroup analysis, the Cox models were also run on the 2 aforementioned subgroups of patients; those that were still consistent at 24 months versus those that were nonconsistent after 12 months and never reinitiated omalizumab.

Statistical significance was assessed with a 2-sided α level of 0.05 or less. All analyses were conducted with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics

Baseline demographics and clinical characteristics of the study population are presented in Table I. A total of 3044 patients

(mean age, 48.5 years; female, 62%) formed the study population. Patients were most likely to be using ICSs (80%), LABAs (65%), SABAs (66%), and leukotriene modifiers (61%) at baseline with a large proportion of patients receiving the fixed-dose combination of LABA+ICS (57%). Sixty-seven percent of study patients had been diagnosed with the extrinsic form of asthma. The most common comorbidity among the study patients was allergic rhinitis (56%). During the 6-month baseline period, patients had a mean $\pm$ SD of 17.4 ± 9.8 all-cause pharmacy claims with an average of 8.0 ± 4.9 asthma-related pharmacy claims. The mean number of all-cause and asthma-related outpatient services was 10.9 ± 6.1 claims and 5.0 ± 3.6 claims, respectively.

Adherence and consistency

The patterns of adherence to and consistency with omalizumab treatment are presented in Table II. Patients had a mean of 10.1 ± 5.2 omalizumab dispensings over the landmark period with a mean of 35.6 ± 17.1 days between dispensings. The mean PDC of $68.7\% \pm 26.6$ resulted in 47% patients being adherent to their omalizumab treatment throughout the landmark period. A total of 1179 (39%), 530 (17%), and 398 (13%) patients were consistent at months 12, 18, and 24, respectively. Of the 2012 patients who were eligible for the entire 24 months, 1614 (80%) were nonconsistent with ≥ 1 gap of 28 days, of which 1074 (53%) discontinued omalizumab during the 24-month period and never reinitiated.

Omalizumab consistency and asthma control

The landmark analyses are presented in Table III. Among the 2012 patients eligible for the entire 24-month period, patients consistent with omalizumab at month 12 ($n = 801$) were less likely to have an uncontrolled asthma event during the follow-up period with only 48.8% of patients experiencing an uncontrolled asthma event compared with 54% in the nonconsistent subgroup ($n = 1211$; $P = .02$). Results were similar when a logistic regression model was run to control for potential differences in baseline characteristics, whereby patients consistent at month 12 were found to be 27% less likely to have an uncontrolled asthma event (odds ratio = 0.73; 95% CI, 0.60-0.89; $P < .01$). In addition, consistency with omalizumab treatment at 12 months

TABLE I. Baseline demographics and clinical characteristics

	Patients receiving omalizumab (n = 3044)
Age at index date (y), mean $\pm$ SD [median]	48.5 $\pm$ 15.7 [50.0]
Age categories, no. (%)	
12-17 y	196 (6)
18-44 y	881 (29)
45-64 y	1598 (53)
≥ 65 y	369 (12)
Female, no. (%)	1898 (62)
Region, no. (%)	
North Central	757 (25)
North East	369 (12)
South	1386 (46)
West	520 (17)
Unknown	12 (0.4)
Year of index date, no. (%)	
2003	31 (1)
2004	342 (11)
2005	516 (17)
2006	460 (15)
2007	470 (15)
2008	506 (17)
2009	459 (15)
2010	260 (9)
Baseline asthma medication,* no. (%)	
ICS	2442 (80)
Fixed-dose combination (LABA + ICS)	1740 (57)
LABA	1964 (65)
Fixed-dose combination (LABA + ICS)	1740 (57)
SABA	2011 (66)
Fixed-dose combination (SABA + anticholinergics)	353 (12)
Anticholinergics	840 (28)
Fixed-dose combination (SABA + anticholinergics)	353 (12)
OCS	1479 (49)
Leukotriene modifiers	1848 (61)
Methylxanthines	275 (9)
Mast cell stabilizers	76 (3)
Quan-Charlson comorbidity index,* mean $\pm$ SD [median]	0.30 $\pm$ 0.7 [0.0]
Extrinsic asthma, no. (%)	2034 (67)
Comorbidities,* no. (%)	
Allergic rhinitis	1696 (56)
Respiratory infections	978 (32)
Chronic sinusitis	621 (20)
Acute sinusitis	462 (15)
Chronic obstructive pulmonary disease	353 (12)
Resource utilization,* mean $\pm$ SD [median]	
Pharmacy claims	
All pharmacy claims	17.4 $\pm$ 9.8 [16.0]
Asthma medication claims [†]	8.0 $\pm$ 4.9 [8.0]
All medical services	
Outpatient services	10.9 $\pm$ 6.1 [10.0]

(Continued)

TABLE I. (Continued)

	Patients receiving omalizumab (n = 3044)
ED visits	0.3 $\pm$ 1.3 [0.0]
Hospitalizations	0.2 $\pm$ 0.5 [0.0]
Length of hospitalization stay (d)	4.2 $\pm$ 3.8 [3.0]
Other services [‡]	15.8 $\pm$ 10.6 [14.0]
Asthma-related medical services* [§]	
Outpatient services	5.0 $\pm$ 3.6 [5.0]
ED visits	0.1 $\pm$ 0.5 [0.0]
Hospitalizations	0.1 $\pm$ 0.3 [0.0]
Length of hospitalization stay (d)	4.1 $\pm$ 2.9 [3.8]
Other services [‡]	6.2 $\pm$ 4.9 [5.0]

*Evaluated during the baseline period defined as 6 months before the index date.

[†]Defined as pharmacy claims for LABAs, SABAs, ICSs, OCSs, leukotriene modifiers, methylxanthines, mast cell stabilizers, anticholinergics, monoclonal antibodies, or fixed-dose combinations (LABA + ICS, SABA + anticholinergics).[‡]Other services include services for long-term care, skilled nursing facilities, rehabilitation centers, laboratory, and tests.[§]Defined as services associated with a diagnosis of asthma (ICD-9, 493.xx).**TABLE II.** Omalizumab adherence and consistency

	Value
Total no. of patients receiving omalizumab	3044
Treatment patterns during landmark period (months 1-12)	
No. of omalizumab dispensings, mean $\pm$ SD [median]	10.1 $\pm$ 5.2 [11]
1 dispensing, no. (%)	108 (4)
2-5 dispensings, no. (%)	503 (17)
6-10 dispensings, no. (%)	887 (29)
11-13 dispensings, no. (%)	1143 (38)
≥ 14 dispensings, no. (%)	403 (13)
No. of days between dispensings, mean $\pm$ SD [median]	35.6 $\pm$ 17.1 [32]
Adherence during landmark period (months 1-12)* [†]	
PDC (%), mean $\pm$ SD [median]	68.7 $\pm$ 26.6 [78]
Adherence, no. (%)	1441 (47)
Consistency, [‡] no. (%)	
At 12 mo	1179 (39)
At 18 mo	530 (17)
At 24 mo	398 (13)
Patients eligible at 24 mo (n = 2012), no. (%)	
Consistency* [‡]	
At 12 mo	801 (40)
At 24 mo	398 (20)
Patients with ≥ 1 gap of 28 d at 24 mo	1614 (80)
Patients reinitiating omalizumab during the 24-mo period	540 (27)
Patients never reinitiating omalizumab during the period	1074 (53)
Patients nonconsistent at 12 mo who did not reinitiate omalizumab during the 24 mo	762 (38)

*For omalizumab medical claims, a supply of 28 days was assumed.

[†]Patients with a PDC $\geq 80\%$ were categorized as adherent, whereas patients with a PDC $< 80\%$ were categorized as nonadherent.[‡]Patients who had no excessive gaps (≥ 28 days) over the specified time period were categorized as consistent, whereas patients with ≥ 1 excessive gap were considered nonconsistent.

TABLE III. Consistent omalizumab treatment and asthma control: a landmark analysis

	Patients eligible ≥ 24 mo after index date (n = 2012)			Subgroup of patients consistent at 24 mo vs those nonconsistent at 12 mo that never reinitiated omalizumab (n = 1160)		
	Consistent at 12 mo (n = 801)	Nonconsistent at 12 mo (n = 1211)	P value	Consistent at 24 mo* (n = 398)	Discontinued at 12 mo and never reinitiated* (n = 762)	P value
Uncontrolled asthma, [†] no. (%)	391 (49)	654 (54)	.02	174 (44)	421 (55)	<.01
Other asthma-related events [†]						
Patients with ≥ 1 asthma-related ED visit, no. (%)	41 (5)	104 (9)	<.01	12 (3)	64 (8)	<.01
No. of asthma-related ED visits, mean $\pm$ SD [median]	0.064 $\pm$ 0.3 [0]	0.129 $\pm$ 0.5 [0]	<.01	0.038 $\pm$ 0.3 [0]	0.126 $\pm$ 0.5 [0]	<.01
Patients with ≥ 1 asthma-related hospitalization, no. (%)	81 (10)	136 (11)	.43	32 (8)	85 (11)	.09
No. of asthma-related hospitalizations, Mean $\pm$ SD [median]	0.131 $\pm$ 0.4 [0]	0.182 $\pm$ 0.6 [0]	.03	0.106 $\pm$ 0.4 [0]	0.173 $\pm$ 0.6 [0]	.02
Patients with ≥ 6 claims for SABAs, no. (%)	109 (14)	195 (16)	.13	50 (13)	122 (16)	.12
No. of SABA claims, mean $\pm$ SD [median]	2.342 $\pm$ 3.3 [1]	2.792 $\pm$ 4.1 [1]	<.01	2.168 $\pm$ 3.3 [1]	2.836 $\pm$ 4.1 [1]	<.01
Patients with ≥ 2 pharmacy claims for OCSs, no. (%)	315 (39)	526 (43)	.07	142 (36)	333 (44)	<.01
No. of OCS claims, mean $\pm$ SD [median]	1.880 $\pm$ 2.7 [1]	2.339 $\pm$ 3.1 [1]	<.01	1.648 $\pm$ 2.7 [1]	2.446 $\pm$ 3.2 [1]	<.01

*Patients consistent with omalizumab at 12 months that were still consistent at 24 months were compared with the patients who were not consistent at 12 months and never reinitiated omalizumab during the follow-up period.

[†]Evaluated from month 13 through 24.

was associated with a 51% reduction in the mean number of asthma-related ED visits per patient (consistent vs nonconsistent, 0.064 ± 0.3 vs 0.129 ± 0.5 ; $P < .01$) and a 28% reduction in asthma-related hospitalizations (0.131 ± 0.4 vs 0.182 ± 0.6 ; $P = .03$). Results were more pronounced between the subgroup of patients consistent at 24 months (n = 398) and those nonconsistent at 12 months that never reinitiated omalizumab (n = 762), where consistency was associated with a 70% reduction in the mean number of asthma-related ED visits (consistent vs nonconsistent, 0.038 ± 0.3 vs 0.126 ± 0.5 ; $P < .01$) and a 39% reduction in asthma-related hospitalizations (0.106 ± 0.4 vs 0.173 ± 0.6 ; $P = .02$).

A multivariate examination of the effect of time-varying omalizumab consistency in Cox regression models on time to uncontrolled asthma is presented in Table IV. In model 1, omalizumab consistent versus nonconsistent treatment was significantly associated with a lower risk for uncontrolled asthma events (HR = 0.76; 95% CI, 0.69-0.83; $P < .01$). A similar result was observed when the dependent variable was restricted to the time to the first asthma-related ED visit or hospitalization (HR = 0.68; 95% CI, 0.61-0.77; $P < .01$). Furthermore, results remained similar when the same models were run on the subgroups of patients consistent with omalizumab at 24 months versus those nonconsistent at 12 months never reinitiating (time to uncontrolled asthma: HR = 0.75; 95% CI, 0.66-0.84; $P < .01$; time to first asthma-related ED visit or hospitalization: HR = 0.70; 95% CI, 0.58-0.84; $P < .01$).

DISCUSSION

This retrospective cohort study established a statistically significant association between consistent omalizumab treatment and better asthma control among responders to omalizumab.

Consistent omalizumab treatment at 12 months (39% of patients) was associated with a 51% reduction in the mean number of asthma-related ED visits and a 28% reduction in asthma-related hospitalizations, respectively. After adjusting for confounders, omalizumab consistency versus nonconsistency was significantly associated with a lower risk of uncontrolled asthma events (24% reduction) and asthma-related ED visits or hospitalizations (32% reduction).

The landmark and time-to-event frameworks were chosen in this study to examine the temporal relation between asthma control and consistent omalizumab treatment, whereby insufficient treatment consistency must precede the asthma uncontrolled events to infer causality. Hence, the possible causality between asthma control and consistent omalizumab treatment could be assessed. The subgroup analysis contrasted 2 different groups of patients: those that were consistent throughout the study versus those that were not consistent at month 12 and never reinitiated. This allowed an assessment of the effect of excluding from the consistent cohort the patients that eventually discontinued omalizumab during the follow-up period and from the nonconsistent cohort the patients that reinitiated omalizumab during the follow-up period (ie, patients who crossed over). Differences found between these 2 groups in the landmark analysis were systematically more pronounced than in the base case. This suggests that the use of omalizumab for longer periods is also associated with reduced asthma uncontrolled events.

Poor adherence to treatment of chronic disease is associated with poor health outcomes.²⁰ The main barriers to adherence in therapy-related interventions have been reported as dose frequency and incidence of side effects. A study by Broder et al¹⁵ suggested that injected medications may have advantages in adherence to asthma treatment. For instance, the PDC of ICSs or LABAs, in the population of that current analysis, was 40%

TABLE IV. Effect of omalizumab treatment on asthma control using time-varying Cox regression models

	Model 1		Model 2	
	Time to uncontrolled asthma		Time to first asthma-related ED visit or hospitalization	
	HR estimate (95% CI)	P value	HR estimate (95% CI)	P value
Omalizumab consistency (ref: omalizumab nonconsistent)*	0.76 (0.69-0.83)	<.01	0.68 (0.61-0.77)	<.01
Model based on subgroups [†]				
Omalizumab consistency (ref: omalizumab nonconsistent)*	0.75 (0.66-0.84)	<.01	0.70 (0.58-0.84)	.01
Age at index date	1.00 (1.00-1.00)	.77	1.00 (0.99-1.00)	.09
Female (ref: male)	1.04 (0.95-1.14)	.37	1.14 (1.03-1.27)	.01
Region (ref: South)				
North Central	1.13 (1.02-1.25)	.02	0.98 (0.86-1.11)	.73
North East	1.03 (0.89-1.18)	.69	0.97 (0.83-1.14)	.73
West	0.93 (0.83-1.05)	.27	1.08 (0.93-1.24)	.32
Year of index date (ref = 2010)				
2003	0.46 (0.29-0.71)	<.01	0.21 (0.12-0.38)	<.01
2004	0.57 (0.48-0.69)	<.01	0.31 (0.25-0.38)	<.01
2005	0.52 (0.44-0.61)	<.01	0.18 (0.15-0.22)	<.01
2006	0.42 (0.35-0.50)	<.01	0.17 (0.14-0.21)	<.01
2007	0.48 (0.40-0.57)	<.01	0.21 (0.17-0.25)	<.01
2008	0.58 (0.50-0.69)	<.01	0.29 (0.24-0.34)	<.01
2009	0.62 (0.53-0.73)	<.01	0.38 (0.32-0.45)	<.01
Baseline asthma medication (ref: no)				
LABA	0.80 (0.66-0.96)	.02	0.74 (0.58-0.93)	.01
SABA	1.26 (1.14-1.40)	<.01	1.07 (0.94-1.20)	.30
ICS	1.63 (1.41-1.87)	<.01	1.11 (0.94-1.31)	.22
OCS	0.95 (0.87-1.04)	.26	0.95 (0.85-1.05)	.32
Leukotriene modifiers	0.98 (0.89-1.08)	.72	0.99 (0.88-1.11)	.80
Methylxanthines	1.29 (1.11-1.49)	<.01	1.19 (1.00-1.42)	.05
Mast cell stabilizers	1.12 (0.85-1.46)	.42	0.90 (0.64-1.27)	.55
Anticholinergics	1.00 (0.88-1.13)	.95	0.96 (0.83-1.12)	.59
Fixed-dose combination				
LABA + ICS	0.89 (0.74-1.06)	.18	1.21 (0.96-1.52)	.10
SABA + anticholinergics	1.15 (0.98-1.35)	.08	1.27 (1.05-1.53)	.01
Quan-Charlson comorbidity index	1.12 (1.05-1.18)	<.01	1.13 (1.06-1.20)	<.01
Comorbidities (ref: no)				
Extrinsic asthma	1.02 (0.93-1.12)	.69	0.99 (0.89-1.11)	.87
Allergic rhinitis	0.82 (0.75-0.90)	<.01	0.91 (0.82-1.01)	.08
Respiratory infections	1.08 (0.96-1.21)	.21	1.11 (0.97-1.26)	.14
Chronic sinusitis	1.05 (0.95-1.17)	.34	0.95 (0.84-1.09)	.47
Acute sinusitis	0.96 (0.82-1.11)	.57	0.86 (0.72-1.02)	.09
Chronic obstructive pulmonary disease	1.20 (1.05-1.38)	.01	1.17 (1.00-1.38)	.05
Asthma-related resource use				
No. of asthma pharmacy claims	1.06 (1.05-1.07)	<.01	1.00 (0.99-1.01)	.92
No. of outpatient services	1.01 (1.00-1.02)	.10	1.04 (1.02-1.05)	<.01
No. of ED visits	1.31 (1.22-1.42)	<.01	1.49 (1.38-1.61)	<.01
No. of hospitalizations	1.66 (1.45-1.91)	<.01	1.72 (1.48-2.01)	<.01
No. of other services [‡]	1.01 (1.00-1.02)	<.01	1.00 (0.99-1.01)	.53

*The time varying variable of omalizumab consistency was defined on the basis of the date of failure of treatment consistency, which was defined as the date corresponding to the end of the day supply (28 days) of the last dispensing before a gap of ≥ 28 days.

[†]Estimated from a separate model in which the subset of patients with omalizumab at 12 months that were still consistent at 24 months were compared with the patients who were not consistent at 12 months and never reinitiated omalizumab during the follow-up period (n = 1160).

[‡]Other services include services for long-term care, skilled nursing facilities, rehabilitation centers, laboratory, and tests.

(analysis not shown) compared with the 69% reported here for omalizumab. This is possibly because omalizumab is injected and thus requires a physician office visit that may make patients less likely to skip doses.¹⁵ In addition, omalizumab is only taken

every 2 to 4 weeks, whereas most other controller medications are taken daily.¹⁵

The overall levels of both adherence and consistency reported in this study are similar to levels reported in a number of recent

reports. The study by Broder et al¹⁵ reported a mean adherence of 54% after 1 year of observation. This is slightly higher than the proportion (47%) reported in this study, because included patients had already continuously been using omalizumab for ≥ 6 months before the index date.¹⁵ Similar adherence rates have been reported for ICSs.^{21,22} The less than ideal rate of consistent omalizumab treatment found in this study suggests that physicians should strive for optimal adherence with omalizumab to improve the effectiveness of this treatment regimen.

This analysis was designed to analyze the effect of consistent omalizumab treatment on asthma control among responders to omalizumab. Because of the absence of medical chart information in the database used, the criterion of ≥ 6 months of continuous omalizumab use before the index date was imposed as a proxy measure to identify responders to omalizumab. However, this criterion does not guarantee that patients who use omalizumab for 6 months were all responders nor that the patients who discontinued omalizumab in the first 6 months did not respond to the medication. Nevertheless, it ensures that patients included in the analysis were exposed to the medication for a certain duration, suggesting that the medication was effective. In addition, 28 days of supply was assumed for medical claims even though omalizumab can be indicated for administration every 2 or 4 weeks. Therefore, patients receiving omalizumab every 2 weeks need to miss 3 doses before being identified as nonconsistent. The effect of this assumption on the results is unclear; however, only 13% of patients had 14 omalizumab dispensings or more during the observation period, suggesting that most patients received their medication monthly.

Despite the thorough study protocol and design, this study had several limitations. First, administrative claims data may be subject to inaccuracies, and missing data and pharmacy dispensing claims may not reflect patients' actual compliance to the medications. The database used in this research is more representative of the South and North Central regions of the United States, which may explain the greater percentage of patients who used omalizumab identified in these regions (as seen in Table I). In addition, claims data tend to lack certain information such as reasons for treatment and disease severity, which would generally be readily available in a clinical trial. For example, because only 67% of patients had a diagnosis for extrinsic asthma during the baseline period, even if omalizumab is indicated for patients with allergic asthma, this 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 diagnosis code (eg, 493) while recording the claim. In addition, reasons for prescribing were not available; thus, it was not possible to differentiate the reported asthma medication use from medications received for other conditions (eg, chronic obstructive pulmonary disease). Likewise, reasons for discontinuation were not available. Because of the retrospective nature of a claims analysis, it was also impossible to confirm the causality of the association between omalizumab and uncontrolled asthma outcomes; thus, the results of this study may be due to other factors (eg, treatment consistency to other controller medications). However, health claims data remain a valuable source of information because they comprise a fairly valid, large sample of real-world practice data and allow treatment patterns to be examined without intervention bias.

On the basis of health insurance claims, this large observational study showed that consistent omalizumab treatment was

associated with significant reductions in ED visits and hospitalizations. Overall, the observed less-than-ideal rate of consistent omalizumab treatment suggests that physicians should strive for optimal adherence with omalizumab to improve the effectiveness of this treatment regimen.

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