

PHARMACOTHERAPY

# Concomitant Asthma Medication Use by Patients Receiving Omalizumab 2003–2008

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**Objective.** To examine patterns of omalizumab use in the first 5 years of its availability. **Methods.** Our study comprised a series of descriptive retrospective cohort analyses using healthcare claims data. The study population comprised patients of any age who had omalizumab claims in the 5 years after 1 July 2003, and we created five 1-year cohorts from this population. Each cohort included patients continuously enrolled for at least 12 months with  $\geq 2$  omalizumab claims during the year. Cohorts contained between 302 and 1382 unique omalizumab users, and over 99% of patients with an omalizumab claim had at least one asthma diagnosis. **Results.** In all years, the specialty most commonly seen in conjunction with the initial omalizumab prescription was allergy/immunology. In all years, omalizumab was used in conjunction with three or more additional classes of asthma medications at least 70% of the time and with five or more classes at least 33% of the time; the proportion of patients filling omalizumab prescriptions who had no other concomitant classes of asthma medications varied from 4% to 8%. The most common pattern of asthma medication treatment in all years was omalizumab with combination steroids/long-acting beta-agonist inhaler, a leukotriene receptor antagonist, a short-acting beta-agonist inhaler, and at least one course of oral corticosteroids. **Conclusions.** In this study of a large sample of commercial health insurance claims covering the first 5 years after approval of omalizumab, we found that omalizumab was infrequently used as a single agent or without concomitant inhaled corticosteroids, and most omalizumab prescriptions came from specialist physicians.

**Keywords** cohort, guidelines, insurance claims, retrospective

## INTRODUCTION

More than 20 million people have asthma in the United States, and asthma attacks account for half a million hospitalizations per year (1). Omalizumab, the only US Food and Drug Administration (FDA)-approved biological therapy for asthma, is a recombinant DNA-derived humanized IgG1 $\kappa$  monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It is indicated for patients with moderate-to-severe persistent asthma and a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (ICSs) (2). The 2007 Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma, developed by the National Heart Lung and Blood Institute, describes six steps of therapy with the goal of controlling disease symptoms. When asthma is not controlled, the EPR-3 recommends increasing the intensity or “stepping-up” of therapy, using a variety of medications. Patients in whom medium-dose ICSs along with long-acting beta-agonists (LABAs) fail to control symptoms are considered by EPR-3 to be at Step 4, and omalizumab is considered appropriate adjunctive therapy for them (3).

The only biological therapy approved for use in asthma, omalizumab, is indicated for patients with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with ICSs (2). Consistent with this indication, EPR-3 recommends the use of omalizumab when asthma is not controlled with medium-dose ICSs along with LABA inhalers. Specifically, EPR-3 recommends considering omalizumab in Step 5 or 6 in conjunction with high-dose ICSs/LABAs. We conducted this analysis to examine the demographics of patients using omalizumab in the first 5 years of its availability and to describe their use of concomitant asthma medications.

## METHODS

The study comprised a series of descriptive retrospective cohort analyses using healthcare claims data. All analyses used the Ingenix i3 LabRx database, which includes claims for the use of medical services and prescription drugs as well as data on enrollment. The data included detailed information on inpatient admissions as well as medical encounters in a physician’s office, hospital outpatient facility, emergency department, or other outpatient facility. Clinical data such as race/ethnicity, income, weight, and smoking history were not available in the database, nor were laboratory values such as IgE levels. According to the terms of the data use, patients could not be contacted to supply missing information.

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Prescription drug claims included fill date, cost, quantity (e.g., vial number in the case of omalizumab, canisters for inhaled medications), and days of medication supply. For omalizumab, quantity was limited to the number of vials. The data were de-identified, making the study exempt from review by the human subjects protection committee.

The study population comprised patients of any age who had omalizumab claims in the 5 years after 1 July 2003 (omalizumab was approved by the FDA on 20 June 2003). From this population we created five 1-year cohorts, and each cohort included patients continuously enrolled for at least 12 months with  $\geq 2$  omalizumab claims during the year. Patients could have appeared in multiple 1-year cohorts if they met the criteria in more than 1 year. Omalizumab was identified using National Drug Codes (50242004062) and Healthcare Common Procedure Coding System codes (J2357, S0107, C9217). Asthma was defined by an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 493.xx in any position on any claim.

For patients with a first omalizumab claim identified from a medical claim, the specialty of the physician providing the first treatment was identified. In cases where omalizumab was identified through pharmacy claims, no physician specialty information was available. To identify the treating physician specialty in those cases, we reviewed all physician office visits with evaluation/management services within 60 days of the first omalizumab claim and reported the physician specialty recorded on the most proximal claim. Physician specialty was reported as “unknown” if it could not be identified with this method or if it was recorded as “unknown” on the claim. Asthma medications other than omalizumab were categorized into one of eight classes: short-acting beta-agonist (SABA) inhalers, LABAs, ICSs, leukotriene receptor antagonists (LTRAs), mast cell stabilizers, methylxanthines, oral corticosteroids (OCSs), and anticholinergics. Combination products were classified

as two drug classes (e.g., salmeterol/fluticasone was classified as both a ICS and a LABA).

This was a descriptive cohort study. Means and SDs were reported for continuous variables, and counts and percentages were reported for categorical variables. All data transformations and analyses were performed using SAS<sup>®</sup> version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Between 597 and 2239 unique patients who filled an omalizumab prescription were identified in the database each year. Requiring two omalizumab claims for inclusion eliminated 25% of the 2003 cohort and 9–13% of the 2004–2007 cohorts. The continuous enrollment requirement further reduced the groups to between 302 (2003 cohort) and 1382 individuals (2007 cohort) (Figure 1). Over 99% of patients with an omalizumab claim had at least one asthma diagnosis, and 98.5% had three or more omalizumab claims. For all years, the mean age ranged from 43 to 44 years and the proportion of females ranged from 60% to 63%. The proportion of patients who were new users of omalizumab declined each year, from 100% in 2003 (the year of approval) to 40% in 2005 and 28% in 2007 (Table 1).

In all years, the specialty most commonly seen in conjunction with the initial omalizumab prescription was allergy/immunology. The proportion whose initial prescription came from an allergist/immunologist decreased from 45% in 2003 to 34% in 2007. Pulmonology was the next most common initial treating specialty, and this also decreased from 17.5% in 2003 to 12.8% in 2007. The proportion of patients whose initial treating physician was a primary care provider (family medicine or internal medicine) increased from 17.2% in 2003 to 22.5% in 2007 (Figure 2).

In all years, omalizumab was used in conjunction with three or more additional classes of asthma medications (e.g., LABAs, ICSs, LTRAs, and SABAs) in at least 70% of patients. The proportion of patients who used

	2003 Cohort 1 July 2003 – 30 June 2004	2004 Cohort 1 July 2003 – 30 June 2005	2005 Cohort 1 July 2003 – 30 June 2006	2006 Cohort 1 July 2003 – 30 June 2007	2007 Cohort 1 July 2003 – 30 June 2008
Omalizumab user	N = 597	N = 1550	N = 2045	N = 2239	N = 2163
↓					
With $\geq 2$ omalizumab claims	N = 448	N = 1347	N = 1828	N = 1984	N = 1976
↓					
Continuously enrolled	N = 302	N = 970	N = 1301	N = 1361	N = 1382

FIGURE 1.—Selection of omalizumab users for 2003, 2004, 2005, 2006, and 2007 cohorts.

Note: Omalizumab users defined as patients filling at least one prescription during the study year.

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TABLE 1.—Demographics of patients with omalizumab claims, stratified by 1-year cohort.

		2003	2004	2005	2006	2007
Patient count		302	970	1,301	1,361	1,382
Age (years)	Mean	43.9	42.8	42.9	43.5	44.1
	(SD)	(13.5)	(14.4)	(14.6)	(14.7)	(14.9)
0–11	Number	1	7	13	16	17
	(Column%)	(0.3)	(0.7)	(1.0)	(1.2)	(1.2)
12–17	Number	21	84	114	109	95
	(Column%)	(7.0)	(8.7)	(8.8)	(8.0)	(6.9)
18+	Number	280	879	1174	1236	1270
	(Column%)	(92.7)	(90.6)	(90.2)	(90.8)	(91.9)
Female	Number	182	592	805	849	866
	(%)	(60.3)	(61.0)	(61.9)	(62.4)	(62.7)
New users	Number	302	601	525	411	386
	(%)	(100.0)	(62.0)	(40.4)	(30.2)	(27.9)

Note: SD, standard deviation.

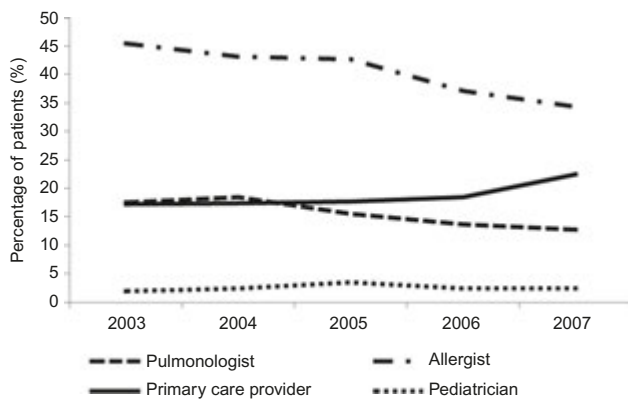


FIGURE 2.—Proportion of patients with initial treating physician specialty, 2003–2007. For patients with a first omalizumab claim identified from a medical claim, the specialty of the physician providing the first treatment was identified. In cases where omalizumab was identified through pharmacy claims, no physician specialty information was available. To identify the treating physician specialty in those cases, we reviewed all physician office visits with evaluation/management services within 60 days of the first omalizumab claim and reported the physician specialty recorded on the most proximal claim.

omalizumab in conjunction with three or more such classes varied from 83% in 2003 to 70% in 2007. Omalizumab was used in conjunction with five or more classes by between 33% (year 2007) and 48% (year 2003) of patients. The proportion of patients filling omalizumab prescriptions who had no other concomitant classes of asthma medications varied from 4% in 2003 to 8% in 2007 (Table 2).

The most common pattern of asthma medication treatment in all years was omalizumab with combination steroids/LABA, a LTRA, a SABA, and at least one course of OCSs. This pattern was seen in 13–19% of patients, depending on the year. Treatment regimens that included omalizumab in conjunction with steroids and LABAs comprised 8 of the 10 most common patterns each year (Table 3). In 71.9% of cases, omalizumab was used in conjunction with ICSs, in 62.5% of cases in conjunction with both ICSs and LABAs, and in 23.8% of cases in conjunction with high-dose ICSs, LABAs, and LTRAs.

## DISCUSSION

Omalizumab was used in conjunction with similar combinations of medications over the 5 years of the study, both in the 4 years before and in the 1 year after the EPR-3 guidelines became available. Specifically, nearly all omalizumab users had multiple asthma diagnoses. Most omalizumab prescriptions were filled by patients who also filled prescriptions for ICSs and LABAs. Furthermore, omalizumab prescriptions came from specialist physicians in approximately 80% of cases. Eight of the 10 most common omalizumab treatment regimens included both ICSs and LABAs, and in 62.5% of cases overall these three medications were combined, as is recommended by EPR-3.

Although concordance with expert guidelines varies widely, the appropriateness of omalizumab use appears to be consistent with the quality of care for asthma patients reported in other studies. We previously studied asthma in a large group of patients and found that 12–41% had their medications appropriately increased in response to evidence of poor disease control (4). Schuster and colleagues (5) found quality indicators were

TABLE 2.—Number of asthma patients using additional classes of medications in conjunction with omalizumab, stratified by 1-year cohort.

Number of concomitant classes of medications	Cohort				
	2003 (N = 302)	2004 (N = 970)	2005 (N = 1,301)	2006 (N = 1,361)	2007 (N = 1,382)
0	12 (4.0)	73 (7.5)	92 (7.1)	95 (7.0)	114 (8.2)
1	19 (6.3)	74 (7.6)	95 (7.3)	110 (8.1)	123 (8.9)
2	21 (7.0)	103 (10.6)	147 (11.3)	154 (11.3)	177 (12.8)
3	33 (10.9)	150 (15.5)	212 (16.3)	205 (15.1)	229 (16.6)
4	71 (23.5)	217 (22.4)	259 (19.9)	311 (22.9)	281 (20.3)
5	80 (26.5)	213 (22.0)	309 (23.8)	298 (21.9)	290 (21.0)
≥6	66 (21.9)	140 (14.4)	187 (14.4)	188 (13.8)	168 (12.2)

Note: The eight classes of medications were as follows: short-acting beta-agonist (SABA) inhalers, long-acting beta-agonist (LABA) inhalers, inhaled corticosteroids (ICSs), leukotriene receptor antagonists (LTRAs), mast cell stabilizers, methylxanthines, oral corticosteroids (OCSs), and anticholinergics.

TABLE 3.—Top 10 asthma medication patterns during the identification period, stratified by 1-year cohort.

Medications used	
	Number (%)
<b>2003</b> (N = 302)	
ICS + LABA + LTRA + OCS + SABA	58 (19.21)
ICS + LABA + OCS + SABA	32 (10.60)
ICS + LABA + LAMA + LTRA + OCS + SABA	27 (8.94)
ICS + LABA + LTRA + MX + OCS + SABA	17 (5.63)
ICS + LABA + LTRA + SABA	16 (5.30)
ICS + LABA + LAMA + LTRA + MX + OCS + SABA	14 (4.64)
Omalizumab alone	12 (3.97)
OCS	10 (3.31)
ICS + LABA + LTRA + OCS	9 (2.98)
ICS + LABA + LTRA	7 (2.32)
All other	100 (33.11)
<b>2004</b> (N = 970)	
ICS + LABA + LTRA + OCS + SABA	133 (13.71)
Omalizumab alone	73 (7.53)
ICS + LABA + LTRA + SABA	73 (7.53)
ICS + LABA + OCS + SABA	71 (7.32)
ICS + LABA + LAMA + LTRA + OCS + SABA	68 (7.01)
ICS + LABA + SABA	43 (4.43)
OCS + SABA	34 (3.51)
ICS + LABA + LTRA + MX + OCS + SABA	29 (2.99)
OCS	29 (2.99)
ICS + LABA + LTRA	28 (2.89)
All other	389 (40.10)
<b>2005</b> (N = 1301)	
ICS + LABA + LTRA + OCS + SABA	201 (15.45)
ICS + LABA + LAMA + LTRA + OCS + SABA	107 (8.22)
Omalizumab alone	92 (7.07)
ICS + LABA + LTRA + SABA	85 (6.53)
ICS + LABA + OCS + SABA	75 (5.76)
ICS + LABA + SABA	52 (4.00)
ICS + LABA + LAMA + OCS + SABA	46 (3.54)
ICS + LABA + LTRA	44 (3.38)
SABA	43 (3.31)
ICS + LABA	41 (3.15)
All other	515 (39.58)
<b>2006</b> (N = 1361)	
ICS + LABA + LTRA + OCS + SABA	186 (13.67)
ICS + LABA + LAMA + LTRA + OCS + SABA	107 (7.86)
Omalizumab alone	95 (6.98)
ICS + LABA + LTRA + SABA	85 (6.25)
ICS + LABA + OCS + SABA	83 (6.10)
ICS + LABA + LTRA + OCS	49 (3.60)
ICS + LABA + SABA	47 (3.45)
ICS + LABA	45 (3.31)
OCS + SABA	39 (2.87)
ICS + LABA + LAMA + OCS + SABA	37 (2.72)
All other	588 (43.20)
<b>2007</b> (N = 1382)	
ICS + LABA + LTRA + OCS + SABA	182 (13.17)
Omalizumab alone	114 (8.25)

(Continued)

TABLE 3.—(Continued).

Medications used	
	Number (%)
<b>2007</b> (N = 1382)	
ICS + LABA + LAMA + LTRA + OCS + SABA	97 (7.02)
ICS + LABA + OCS + SABA	77 (5.57)
ICS + LABA + LTRA + SABA	68 (4.92)
OCS + SABA	52 (3.76)
OCS	51 (3.69)
ICS + LABA + SABA	49 (3.55)
ICS + LABA + LTRA	43 (3.11)
ICS + LABA	42 (3.04)
All other	607 (43.92)

Notes: ICSs, inhaled corticosteroids; LABA, long-acting beta-agonist inhalers; LAMA, long-acting anticholinergics; LTRA, leukotriene receptor antagonists; MCSs, mast cell stabilizers; MXs, methylxanthines; OCSs, oral corticosteroids; SABA, short-acting beta-agonist inhalers. "All other combinations" comprises a wide variety of medication combinations, with each combination used by <3% of patients.

followed in 30–45% of asthma cases, whereas McGlynn et al. (6) reported asthma patients received 53.5% of recommended care. According to the National Committee for Quality Assurance, physicians in commercial health plans prescribed at least one asthma controller medication to 92% of asthma patients in 2008 (7).

In conditions other than asthma, concordance of care with expert recommendations is also imperfect and variable. In a study examining a wide variety of acute and chronic conditions, McGlynn et al. (6) reported that American adults receive 69% of recommended medications. Studying California Medicaid recipients, Nichol et al. (8) reported that medication-prescribing practices were in line with clinical guidelines between 57% and 75% of the time, depending on the condition being treated. In a national study of commercially insured patients with heart failure, 57% received appropriate pharmacological treatment (9).

Almost all of the patients who received omalizumab had multiple asthma diagnoses, making it unlikely that omalizumab was being used for other indications. In this study, 80% of omalizumab prescriptions appeared to be from specialists, which is consistent with the EPR-3 recommendations. However, one of this study's limitations was that most omalizumab claims were pharmacy rather than medical claims, and these claims do not carry information on the prescriber's specialty. For these cases we assumed that the physician seen most proximal to the first omalizumab claim was the prescriber.

This study had other limitations. Most of the care we studied occurred before EPR-3 was released, which likely biased our study toward finding less concordance with these guidelines. However, EPR-3 codified published evidence, so clinicians likely incorporated many of its concepts in their practices before the report was published. EPR-3 recommends that step assignment be based on a clinician's assessment, yet clinical detail is extremely limited in administrative claims data. Omalizumab is

indicated for patients with allergic asthma, but we had no validated claims-based method for determining if a patient's disease had an allergic component. As in all claims studies, we looked at prescription fills, not the actual use of medications. If patients filled but did not use their medications, our results would be biased. In addition, patients may have been miscoded as having asthma when they did not have it. Finally, our findings may not be applicable to populations other than commercially insured ones.

The data we used covered the first 5 years of omalizumab use, with the final data points derived in mid-2008. If practices have changed since then, our findings may no longer be applicable. The FDA-approved prescribing information for omalizumab does not suggest which concomitant medications (other than ICSs) should be used. Our analysis used a stricter standard, comparing care with consensus guidelines rather than with the prescribing information (2). Because some of the care we included occurred before EPR-3 was released, clinicians could not have been trying to comply with these guidelines, which likely biases our results to find less appropriate use.

#### CONCLUSIONS

Our goal was to describe the demographics of, and concomitant medication used by, patients receiving omalizumab in the first 5 years after its approval. Although our study had limitations, it supports the idea that omalizumab is used by an appropriate group of patients with appropriate concomitant medications in most instances. The drug was infrequently used as a single agent or without concomitant ICS, and most use appeared to be initiated by specialists.

#### DECLARATION OF INTEREST

Financial support for this study was provided by Genentech, Inc. Michael Broder and Eunice Chang are employees of Partnership for Health Analytic Research, LLC, which was paid by Genentech for its involvement in this research. James Zazzali is an employee of Genentech. Ashley Yegin was an employee of Genentech at the time of this study. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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