Adherence and persistence with omalizumab and fluticasone/salmeterol within a managed care population

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ABSTRACT

Asthma control requires adherence with pharmacologic therapy. A medication's mode of delivery may affect adherence. The purpose of this study was to compare medication persistence and adherence between patients newly treated with either an inhaled or injected asthma medication. Using a propensity-score–matched retrospective cohort study, we evaluated medication persistence and adherence over 1 year in adult asthma patients newly treated with omalizumab or fluticasone (500 μg)/salmeterol (50 μg) (FSC 500/50). Kaplan-Meier analysis was conducted to compare persistence between users of FSC 500/50 and omalizumab using the log-rank test. We conducted four sensitivity analyses. After propensity matching, the study sample included 213 omalizumab patients and 426 FSC 500/50 patients, with no statistically significant differences between groups on baseline measures. Mean adherence rates were 64.6% for omalizumab and 29.5% for FSC 500/50 ($p < 0.0001$). Fifty-four percent of omalizumab users were persistent at 1 year compared with 18.5% of FSC 500/50 users ($p < 0.0001$). In sensitivity analyses, we stratified patients by evidence of allergy and the results did not change. Adherence was more than twice as high and persistence was almost twice as high among omalizumab compared with FSC 500/50 users. The direction of our findings was consistent across all sensitivity analyses. In both omalizumab and FSC 500/50 cohorts, persistence decreased substantially over 1 year. Our study suggests that injected medications may have advantages in asthma treatment. A comprehensive program to improve adherence should address not just administration route but also patient factors that prevent proper medication use.

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Asthma affects 15–20 million individuals in the United States. More than 5000 deaths are attributed to it each year.[1,2] Asthma can only be controlled if patients adhere to an appropriate medication regimen. Nonadherence results in significant morbidity and mortality and generates higher direct costs, such as hospitalizations and emergency department visits, and higher indirect costs, such as productivity loss.[3,4]

Many things affect adherence, including patient psychological problems, cognitive impairment, inadequate follow-up, medication side effects, lack of patient belief in treatment, lack of patient insight into illness, poor doctor–patient relationship, treatment complexity, and cost.[5–7] A medication's delivery mode also may affect adherence. Patients given oral monotherapy with leukotriene receptor antagonists (LTRAs) are twice as adherent to therapy as those given inhaled corticosteroids or inhaled long-acting β-agonists.[8] Two other studies showed that adherence to an oral LTRA was greater than adherence to inhaled fluticasone (500 μg)/salmeterol (50 μg) (FSC 500/50).[9,10] Adherence among treated patients who had rheumatoid arthritis was higher among those who received medication i.v. than among those treated subcutaneously or orally.[11] It is unknown whether adherence improves in asthma patients who receive injected medications. We evaluated differences in adherence and persistence between injected and inhaled asthma medications, omalizumab and FSC 500/50, respectively, both of which are indicated for persistent moderate-to-severe asthma.

METHODS

Design

We conducted a propensity-score–matched retrospective cohort study to evaluate medication persistence and adherence over 1 year in asthma patients who were newly treated with omalizumab or FSC 500/50. Our study data was from a Health Insurance Portability and Accountability Act–compliant administrative claims database of 8–10 million covered lives and was exempt from human subjects review. This database contained adjudicated pharmacy and medical claims submitted by providers, health care facilities, and pharmacies, and it included information on each

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physician visit, medical procedure, hospitalization, drug dispensed, and test performed. Member enrollment and benefit information were available, as were limited patient, provider, and hospital demographic information. All major regions of the United States were represented.

Patient Selection

We identified patients between 18 and 64 years old who were newly treated with omalizumab or FSC 500/50 during the identification period, May 1, 2004, through April 30, 2005. We excluded patients whose claims had International Classification of Diseases, Clinical Modification (ICD-9-CM) codes for pregnancy or chronic obstructive pulmonary disease or who had no asthma claims during the study period.

The newly prescribed medication was termed the index medication. The index date was defined as the date of the first claim for omalizumab or FSC 500/50 after a no less than 12-month period without index medication use (clean period). New FSC 500/50 users were allowed to have used omalizumab before and *vice versa*. We used a 12-month clean period because some studies have shown that using a 6-month period incorrectly identifies a substantial number of continuing users as new users.[12,13] We examined medication use during two 12-month periods: 12 months before the index date (preindex period) and 12 months after the index date (postindex period). Patients were excluded if they were not continuously enrolled for the entire 24-month observation period.

Baseline Variables

To match new FSC 500/50 users with new omalizumab users, we used baseline characteristics including age, gender, state of residence, specialty of usual-care physician, allergies, select comorbidities, chronic conditions, evidence of poor asthma control, and adherence to controller medications. The data set had no information about socioeconomic status, race, ethnicity, lung function, or symptoms.

Usual-care physician specialty affects treatment patterns,[14,15] so to determine the specialties of the patients' usual physicians, we reviewed office visit claims for evidence of evaluation and management services (defined as those with current procedural terminology codes for office or other outpatient services, office consultations, and preventive medicine services). We identified the specialty of the physician with whom each patient had the most evaluation and management services visits and considered that the patient's usual-care physician.[16]

Because omalizumab is indicated for patients with moderate-to-severe persistent allergic asthma, we looked for evidence of allergy in the database. Such evidence included pharmacy claims with National Drug Code numbers for allergy medications, medical claims with ICD-9-CM codes (in any diagnosis field) for allergic rhinitis or atopic dermatitis, and current procedural terminology codes for allergen immunotherapy.

Because comorbid illness also may affect compliance, we used several categories from the Clinical Classifications Software (CCS) multiple-level disease categories to assess comorbidities. The software was developed by the Agency for Health Care Research and Quality and is a tool for clustering patient diagnoses into 18 main disease categories. We used 12 of 18 categories in the matching process, excluding respiratory system diseases (our disease of interest), complications of pregnancy and childbirth, perinatal conditions, injury and poisoning, symptoms and signs, and residual codes. Because acute and chronic conditions affect patients differently and CCS does not distinguish between them, we used a published methodology based on the CCS to identify each patient's chronic conditions.[17] If a patient had two chronic diagnoses in the same single-level CCS category, they counted as one chronic condition (*e.g.*, hypertension and heart failure counted as one chronic cardiovascular condition).

Patients were classified as having had evidence of poor asthma control if they met any of four conditions during the preindex period: any asthma-related inpatient hospitalization, any asthma-related emergency department visit, two or more oral corticosteroid prescriptions filled, or six or more short-acting β-agonist prescriptions filled. Adherence with one medication might affect adherence with another, so to determine preindex adherence, we calculated the days of supply of all controller medications (inhaled corticosteroids, long-acting β-agonists, and LTRAs) used during the preindex period and divided by 365. With multiple overlapping prescriptions for different controllers, adherence might be >100%, which we prevented by counting a "day of adherence" as one when one or more controllers were in the patient's possession.

Outcome Variables

The outcomes of interest were omalizumab and FSC 500/50 persistence and adherence during the postindex period. We defined persistence as no more than 45 days between the date the study medication was no longer available and the date of the next claim for the same drug. For FSC 500/50, the "days of supply" field from the claims database was used to determine the end of each prescription fill. For omalizumab, each injection was considered a 28-day supply. We also reported the percentage of patients who were persistent by the end of each month of the follow-up period. To determine adherence, we calculated the total days

of supply of the index medication and divided by 365. No adjustment was needed to prevent adherence of >100%, because each patient had only one index medication.

Matching Process

Propensity score analysis is a statistical technique that can be applied to observational data for balancing covariates between two groups.[18,19] We used a logistic regression model to estimate propensity scores. Omalizumab use was the dependent variable, and several baseline measurements were the independent variables. Two-way interactions were considered and included in the final model if significant. The final propensity model included all baseline variables and six interaction terms. In the final cohort, each omalizumab new user was matched with two FSC 500/50 new users.

Statistical Analysis

Baseline measures between the cohorts were compared using chi-square or *t*-tests. The means of postindex adherence rates were compared between matched cohorts using *t*-tests. Kaplan-Meier analysis was conducted to compare persistence between users of FSC 500/50 and omalizumab using the log-rank test. For the survival analysis, patients were censored at the end of last prescription fill, last injection, or study end. We also presented survival plots and the persistence rates for each month.

We conducted four sensitivity analyses. Omalizumab is indicated for patients with moderate-to-severe persistent allergic asthma[20]; therefore, we stratified patients according to evidence of allergy and repeated the main analysis. Omalizumab may be administered every 2 or 4 weeks, depending on patients' immunoglobulin E (IgE) levels.[20] In the second sensitivity analysis, we considered each omalizumab injection a 14-day supply instead of a 28-day supply, biasing the results toward lower omalizumab adherence.

Fluticasone/salmeterol should be titrated to the lowest effective dose,[21] so patients may have switched to a lower strength during the postindex period. In the main analysis, changes to a lower dose were considered cessation of therapy. In the third sensitivity analysis, new FSC 500/50 users who changed to a lower dose were considered still adherent, biasing the results toward greater FSC 500/50 adherence. It is not uncommon for patients to discontinue a medication after the first fill.[12,22] For the fourth sensitivity analysis, we required all new users to have at least two index prescription fills or injections no more than 45 days apart instead of one fill. We repeated the main analysis for each scenario in each case, stratifying the results by evidence of allergy. All tests were two-sided with a 0.05 significance level. All data transformations and statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

We identified 15,220 new users during the identification period, 970 omalizumab and 14,250 FSC 500/50. After exclusions, 3393 new users remained, 318 omalizumab and 3075 FSC 500/50.

The mean age and proportion of female patients were similar (44 ± 10.4 versus 45 ± 11.3; $p = 0.8868$, and 62.9% versus 64.6%, $p = 0.5484$ for omalizumab and FSC 500/50, respectively). There were statistically significant differences in the proportion of omalizumab and FSC 500/50 patients from the various geographic regions. More omalizumab users had allergists (41.2% versus 10.2%) or pulmonologists (16.0% versus 6.0%) as their usual-care physicians than FSC 500/50 users ($p < 0.0001$; Table 1). More omalizumab users had evidence of allergies than FSC 500/50 users (89.0% versus 65.3%; $p < 0.0001$); the average number of chronic diseases was higher among omalizumab than among FSC 500/50 users (4.4 ± 2.5 versus 3.7 ± 2.6, $p < 0.0001$; Table 2); and more omalizumab users had poorer asthma control than FSC 500/50 users (62.3% versus 37.5%; $p < 0.0001$; Table 2). When adherence to baseline controller medications (not the index medication) was compared, omalizumab users had higher baseline adherence than FSC 500/50 users (52.4% versus 33.0%; $p < 0.0001$).

After propensity matching, the final study sample was 639 patients (213 omalizumab and 426 FSC 500/50), and there were no statistically significant differences in preindex demographic, clinical, and utilization parameters (Tables 1 and 2). During the postindex period, mean adherence rates were 64.6% for omalizumab and 29.5% for FSC 500/50 users ($p < 0.0001$). Fifty-four percent of omalizumab users were persistent 1 year after starting therapy compared with 18.5% of FSC 500/50 users ($p < 0.0001$; Table 3; Fig. 1).

In sensitivity analyses, we stratified patients by evidence of allergy and the results did not change (Table 3). When we considered each omalizumab injection as a 14-day instead of a 28-day supply, omalizumab adherence decreased from 64.6 to 32.7% and persistence decreased from 54 to 46.9%. However, omalizumab users still had higher adherence and longer persistence than FSC 500/50 users. When we calculated FSC 500/50 adherence using fills for any of its available strengths, adherence increased to 36.2% from 29.5% and persistence increased to 27% from 18.5%. Omalizumab users remained more adherent (64.6% versus 36.2%, $p < 0.0001$) and more were persistent at study end (54% versus 27%, $p < 0.0001$) than FSC 500/50 users. In our final sensitivity analysis, we required two

Table 1 **Baseline demographics and usual-care physician before and after propensity-score matching**

	Before Matching			After Matching		
	Omalizumab (n = 318; 9.4%)	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 3075; 90.6%)**	**p Value**	**Omalizumab (n = 213; 33.3%)**	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 426; 66.7%)**	**p Value**
	No. of Patients (%) Except as Indicated					
Mean age (yr) (SD)	44 (10.4)	45 (11.3)	0.8868	45 (10.3)	46 (11.0)	0.5378
Age group (yr)						0.3597
18–34	60 (18.9)	586 (19.1)	0.3640	37 (17.4)	70 (16.4)	
35–44	97 (30.5)	853 (27.7)		65 (30.5)	124 (29.1)	
45–54	106 (33.3)	981 (31.9)		73 (34.3)	130 (30.5)	
55–64	55 (17.3)	655 (21.3)		38 (17.8)	102 (23.9)	
Female gender	200 (62.9)	1986 (64.6)	0.5484	147 (69.0)	277 (65.0)	0.3142
Region*			<0.0001			0.9407
South	156 (49.1)	1089 (35.4)		94 (44.1)	180 (42.3)	
Midwest	86 (27.0)	1082 (35.2)		61 (28.6)	132 (31.0)	
West	41 (12.9)	490 (15.9)		31 (14.6)	60 (14.1)	
Northeast	35 (11.0)	414 (13.5)		27 (12.7)	54 (12.7)	
Specialty of usual-care physician			<0.0001			0.9794
Primary care	97 (30.5)	2,014 (65.5)		85 (39.9)	173 (40.6)	
Allergist	131 (41.2)	314 (10.2)		63 (29.6)	117 (27.5)	
Pulmonologist	51 (16.0)	184 (6.0)		32 (15.0)	67 (15.7)	
Other	39 (12.3)	563 (18.3)		33 (15.5)	69 (16.2)	

**Although we show region distribution here, we matched patients by state of residence.*
SD = standard deviation.

Table 2 **Baseline comorbidities, disease control, and asthma medication use before and after matching**

	Before Matching			After Matching		
	Omalizumab (n = 318; 9.4%)	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 3,075; 90.6%)**	**p Value**	**Omalizumab (n = 213; 33.3%)**	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 426; 66.7%)**	**p Value**
	No. of Patients (%) Except as Indicated					
Preindex variable						
Evidence of an allergy	283 (89.0)	2009 (65.3)	<0.0001	182 (85.4)	366 (85.9)	0.8728
Comorbid disease categories						
Infectious and parasitic diseases	149 (46.9)	1139 (37.0)	0.0006	91 (42.7)	187 (43.9)	0.7779
Neoplasms	62 (19.5)	605 (19.7)	0.9394	48 (22.5)	88 (20.7)	0.5846
Endocrine; nutritional; and metabolic diseases and immunity disorders	143 (45.0)	1481 (48.2)	0.2777	100 (46.9)	202 (47.4)	0.9108
Blood and blood forming organs	24 (7.5)	267 (8.7)	0.4911	19 (8.9)	39 (9.2)	0.9224
Mental disorders	74 (23.3)	824 (26.8)	0.1748	58 (27.2)	104 (24.4)	0.4403
Nervous system and sense organs	172 (54.1)	1479 (48.1)	0.0419	115 (54.0)	233 (54.7)	0.8662
Circulatory system	149 (46.9)	1508 (49.0)	0.4580	104 (48.8)	197 (46.2)	0.5376
Digestive system	127 (39.9)	1163 (37.8)	0.4593	89 (41.8)	192 (45.1)	0.4301
Genitourinary system	153 (48.1)	1459 (47.4)	0.8209	108 (50.7)	198 (46.5)	0.3135
Skin and subcutaneous tissue	96 (30.2)	804 (26.1)	0.1201	65 (30.5)	124 (29.1)	0.7131
Musculoskeletal system and connective tissue	177 (55.7)	1,606 (52.2)	0.2432	117 (54.9)	234 (54.9)	0.9999
Congenital anomalies	12 (3.8)	140 (4.6)	0.5225	10 (4.7)	23 (5.4)	0.7045
Mean (SD) no. with chronic conditions	4.4 (2.5)	3.7 (2.6)	<0.0001	4.3 (2.5)	4.4 (2.9)	0.5519
Any poor asthma control	198 (62.3)	1153 (37.5)	<0.0001	120 (56.3)	237 (55.6)	0.8685
Any asthma-related inpatient hospitalization	23 (7.2)	122 (4.0)	0.0061	13 (6.1)	24 (5.6)	0.8107
Any asthma-related emergency department visit	39 (12.3)	183 (6.0)	<0.0001	24 (11.3)	48 (11.3)	0.9999
Filled at least two OCS prescriptions	165 (51.9)	746 (24.3)	<0.0001	99 (46.5)	194 (45.5)	0.8223
Filled at least six SABA prescriptions	85 (26.7)	459 (14.9)	<0.0001	40 (18.8)	86 (20.2)	0.6731
Asthma controller medication use						
Mean (SD) adherence rate (range, 0–100%)	52.4 (35.8)	33.0 (33.8)	<0.0001	44.9 (35.6)	45.5 (36.0)	0.8333

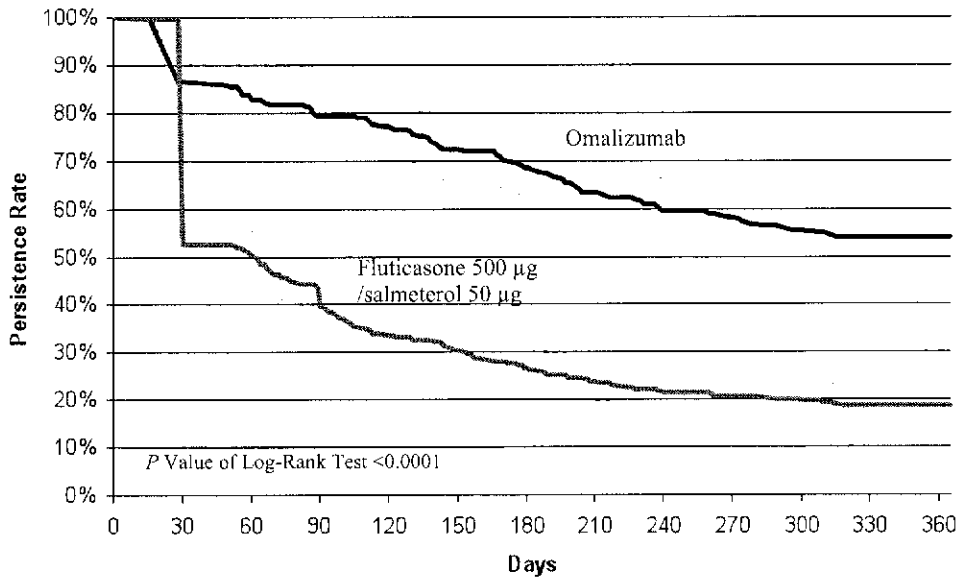
Table 2 **Continued**

	Before Matching			After Matching		
	Omalizumab (n = 318; 9.4%)	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 3,075; 90.6%)**	***p* Value**	**Omalizumab (n = 213; 33.3%)**	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 426; 66.7%)**	***p* Value**
Mean (SD) no. of days covered by any asthma controller medication	191 (131)	121 (123)	<0.0001	164 (130)	166 (132)	0.8333
Any asthma controller medication use	274 (86.2)	2253 (73.3)	<0.0001	174 (81.7)	353 (82.9)	0.7130
Fluticasone/salmeterol 100/50	31 (9.7)	381 (12.4)	0.1697	26 (12.2)	48 (11.3)	0.7266
Fluticasone/salmeterol 250/50	94 (29.6)	1280 (41.6)	<0.0001	71 (33.3)	146 (34.3)	0.8132
ICS	175 (55.0)	1116 (36.3)	<0.0001	101 (47.4)	228 (53.5)	0.1456
LABA	43 (13.5)	170 (5.5)	<0.0001	19 (8.9)	53 (12.4)	0.1845
LTRA	195 (61.3)	1083 (35.2)	<0.0001	113 (53.1)	239 (56.1)	0.4647

ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroid; SABA = short-acting β-agonist.

Table 3 **Postindex adherence and persistence rates after matching**

				Evidence of Allergy					
				No Allergy			Allergy		
	Omalizumab (n = 213)	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 426)**	***p* Value**	**Omalizumab (n = 31)**	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 60)**	***p* Value**	**Omalizumab (n = 182)**	**Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 366)**	***p* Value**
Mean (SD) adherence rate (range, 0–100%)	64.6 (34.1)	29.5 (29.0)	<0.0001	57.7 (36.1)	24.8 (26.2)	<0.0001	65.8 (33.6)	30.2 (29.4)	<0.0001
No. (%) of patients who were persistent by end of study	115 (54.0)	79 (18.5)	<0.0001	14 (45.2)	9 (15.0)	0.0017	101 (55.5)	70 (19.1)	<0.0001



		Month of Follow-up											
		1	2	3	4	5	6	7	8	9	10	11	12
Omalizumab (n = 213)	Persistence rate (%)	86.4	82.6	79.3	77.0	72.3	68.5	63.4	59.6	58.2	55.4	54.0	54.0
	No. of patients continuing therapy	184	176	169	164	154	146	135	127	124	118	115	115
Fluticasone 500 µg/ salmeterol 50 µg (n = 426)	Persistence rate (%)	52.6	50.2	39.9	33.6	30.3	26.5	23.7	21.6	20.9	19.7	18.5	18.5
	No. of patients continuing therapy	224	214	170	143	129	113	101	92	89	84	79	79

Figure 1. Persistence rate and 95% confidence intervals of index medications by end of each follow-up month among matched patients.

or more fills of index medications. Mean adherence rates were 73.8% for omalizumab and 48.5% for FSC 500/50 users ($p < 0.0001$). By study end, 61.5% of omalizumab users were persistent compared with 33.8% of FSC 500/50 users ($p < 0.0001$; Table 4; Fig. 2). Stratifying patients by evidence of allergy resulted in smaller numbers in each group but no change in the direction of the results (Table 4).

DISCUSSION/CONCLUSIONS

In patients with persistent moderate-to-severe asthma, pharmacologic treatment is critical to symptom control.[23] Poor adherence to controller medication may result in more hospitalizations and greater mortality.[24–26] We studied two measures of medication use and found that adherence was more than twice as high and that persistence was almost twice as high among omalizumab than among FSC 500/50 users. Twelve months after initiation of therapy, more than one-half of omalizumab users persisted compared with less than one-quarter of FSC 500/50 users. In both cohorts, persistence decreased substantially over a year, and the direction of our findings was consistent across all sensitivity analyses.

Findings of low adherence with inhaled therapy are consistent with prior research,[3,24,27] although differences in technique make exact comparisons difficult. Our dramatically higher rates of adherence and persistence among omalizumab users have several possible explanations. As other investigators have proposed, it may be that administration route has a significant impact on adherence.[9–11,28] Injected medications require office visits, and patients may be less inclined to skip visits than they are to skip prescription refills. In the

Table 4 **Sensitivity analyses: Adherence and persistence of asthma patients who received omalizumab and fluticasone 500 μg/salmeterol 50 μg**

				Evidence of Allergy					
				No Allergy			Allergy		
	Omalizumab (n = 213)	Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 426)	P Value	Omalizumab (n = 31)	Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 60)	P Value	Omalizumab (n = 182)	Fluticasone (500 μg)/ Salmeterol (50 μg) (n = 366)	P Value
Omalizumab Injection Considered 14-Day Supply									
Mean (SD) adherence rate (range, 0–100%)	32.7 (19.7)	29.5 (29.0)	0.0995	28.0 (18.6)	24.8 (26.2)	0.1267	33.5 (19.8)	30.2 (29.4)	0.5071
No. (%) of patients who were persistent by end of study	100 (46.9)	79 (18.5)	<0.0001	11 (35.5)	9 (15.0)	0.0253	89 (48.9)	70 (19.1)	<0.0001
Use of any Strength of Fluticasone/Salmeterol Considered Adherent									
Mean (SD) adherence rate (range, 0–100%)	64.6 (34.1)	36.2 (32.4)	<0.0001	57.7 (36.1)	28.3 (29.3)	<0.0001	65.8 (33.6)	37.5 (32.8)	<0.0001
No. (%) of patients who were persistent by end of study	115 (54.0)	115 (27.0)	<0.0001	14 (45.2)	12 (20.0)	0.0118	101 (55.5)	103 (28.1)	<0.0001
Two or More Fills of Index Medication Required for Eligibility									
	Omalizumab (n = 148)	Fluticasone 500 μg/ Salmeterol 50 μg (n = 296)	P Value	Omalizumab (n = 23)	Fluticasone 500 μg/ Salmeterol 50 μg (n = 39)	P Value	Omalizumab (n = 125)	Fluticasone 500 μg/ Salmeterol 50 μg (n = 257)	P Value
Mean (SD) adherence rate (range, 0–100%)	73.8 (26.9)	48.5 (29.7)	<0.0001	73.5 (23.8)	45.5 (29.4)	0.0003	73.8 (27.5)	49.0 (29.8)	<0.0001
No. (%) of patients who were persistent by end of study	91 (61.5)	100 (33.8)	<0.0001	13 (56.5)	14 (35.9)	0.1136	78 (62.4)	86 (33.5)	<0.0001

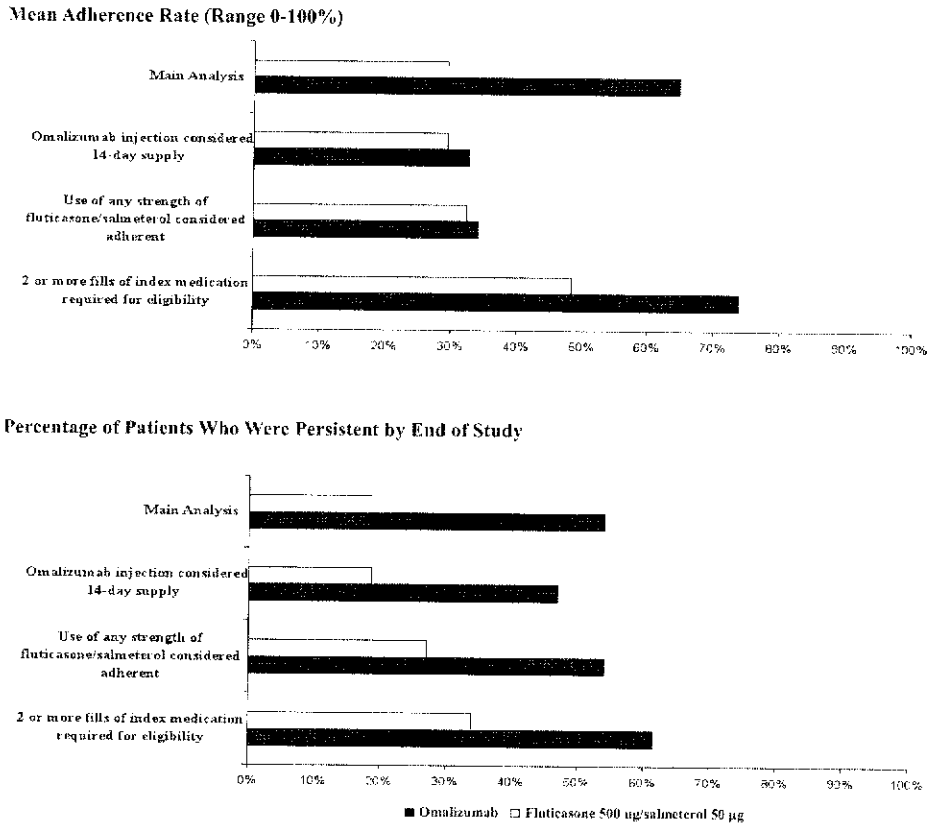


Figure 2. Sensitivity analyses: adherence and persistence of asthma patients who received omalizumab and fluticasone (500 µg)/salmeterol (50 µg).

care of patients with tuberculosis and human immunodeficiency virus, directly observed therapy increases adherence.[29,30] Omalizumab is given every 2–4 weeks, and fluticasone/salmeterol is given daily; greater frequency has been associated with lower adherence in other studies.[3] We had no clinical or satisfaction information that could enable us to distinguish among these explanations.

The differences in adherence between cohorts also may reflect unmeasured differences between groups (*e.g.*, patients receiving omalizumab may have had more severe disease). We tried to make the groups similar at the outset by studying new users of medications indicated for persistent moderate-to-severe asthma. We also used propensity score matching to control for differences, but we could only match on characteristics that were captured in the claims data. Omalizumab is only indicated in patients with evidence of allergy, a subset of all asthma patients. Focusing only on those patients did not change the results. Differences in clinical presentation, physiological measures (*e.g.*, pulmonary function test results), or other characteristics were not part of the data set, and most severity measures require such data. If one cohort was more severe than the other, it is not clear what bias would result. The evidence that severity of illness impacts adherence is limited; most studies suggest it does not.[3,31]

Measurement error also could explain some of our findings. Medication samples are not recorded in claims data, and prescriptions are not filled outside the plan. Because of cost and the need to administer omalizumab in the physician's office, its use may be more completely captured than fluticasone/salmeterol fills, increasing apparent persistence and adherence. On the other hand, fluticasone/salmeterol may be filled more frequently than needed so that devices can be left in several convenient locations. We did not have the resources to confirm these behaviors through chart review or interviews. As in any claims-based study, coding errors could have affected data integrity.

Despite these limitations, we found evidence that adherence and persistence with an injected asthma controller medication are greater than with an inhaled one. Medication adherence is crucial to successful asthma management, and many interventions have been tested to see if they improve adherence and clinical outcomes in patients with asthma. Doubling medication adherence would have ranked as one of the largest effects in a recent review.[32] This should not imply that changing patients' medication from fluticasone/salmeterol to omalizumab would improve out-

comes. Our study was not designed to compare these agents but rather to investigate whether administration route might impact adherence. Our study does suggest that injected medications may have advantages in asthma treatment, but as other investigators have pointed out, effectively improving asthma treatment requires a combination of "pharmacology and psychology."[33] A comprehensive program to improve adherence would have to address not just administration route but patient beliefs and concerns that may prevent them from taking their medications as prescribed.

REFERENCES

1. American Lung Association. Trends in asthma morbidity and mortality May 2005. American Lung Association, New York, 2005.
2. Redd S. Asthma in the United States: Burden and current theories. Environ Health Perspect 110(suppl 4):557–560, 2002.
3. World Health Organization. Adherence to long-term therapies: Evidence for action. World Health Organization, Geneva, 2003.
4. Osterberg L, and Blaschke T. Adherence to medication. N Engl J Med 353:487–497, 2005.
5. Horne R, and Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 47:555–567, 1999.
6. Lacasse Y, Archibald H, Ernst P, and Boulet LP. Patterns and determinants of compliance with inhaled steroids in adults with asthma. Can Respir J 12:211–217, 2005.
7. Soriano JB, Rabe KF, and Vermeire PA. Predictors of poor asthma control in European adults. J Asthma 40:803–813, 2003.
8. Jones C, Santanello NC, Boccuzzi SJ, et al. Adherence to prescribed treatment for asthma: Evidence from pharmacy benefits data. J Asthma 40:93–101, 2003.
9. Bukstein DA, Bratton DL, Firriolo KM, et al. Evaluation of parental preference for the treatment of asthmatic children aged 6 to 11 years with oral montelukast or inhaled cromolyn: a randomized, open-label, crossover study. J Asthma 40:475–485, 2003.
10. Bukstein DA, Henk HJ, and Luskin AT. A comparison of asthma-related expenditures for patients started on montelukast versus fluticasone propionate as monotherapy. Clin Ther 23: 1589–1600, 2001.
11. Harley CR, Frytak JR, and Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care 9(suppl 6):S136–S143, 2003.
12. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: Methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Invest Ophthalmol Vis Sci 48:5052–5057, 2007.
13. Quigley HA, Friedman DS, and Hahn SR. Evaluation of practice patterns for the care of open-angle glaucoma compared with claims data: The Glaucoma Adherence and Persistency Study. Ophthalmology 114:1599–1606, 2007.
14. Laforest L, Van Ganse E, Devouassoux G, et al. Management of asthma in patients supervised by primary care physicians or by specialists. Eur Respir J 27:42–50, 2006.
15. Schatz M, Zeiger RS, Vollmer WM, et al. Development and validation of a medication intensity scale derived from computerized pharmacy data that predicts emergency hospital utilization for persistent asthma. Am J Manag Care 12:478–484, 2006.
16. O'Malley AS, Pham HH, Schrag D, et al. Potentially avoidable hospitalizations for COPD and pneumonia: The role of physician and practice characteristics. Med Care 45:562–570, 2007.
17. Hwang W, Weller W, Ireys H, and Anderson G. Out-of-pocket medical spending for care of chronic conditions. Health Aff (Millwood) 20:267–278, 2001.
18. Rosenbaum P, and Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika 70:41–55, 1983.
19. Rosenbaum P, and Rubin D. Reducing bias in observational studies using subclassifications on the propensity score. J Am Stat Assoc 79:516–524, 1984.
20. Genentech, Inc. Omalizumab (Xolair) prescribing information. South San Francisco, CA; July 2008.
21. GlaxoSmithKline. Advair Diskus prescribing information. Research Triangle Park, NC; April 2008.
22. Ory C, Fontes C, Williams S, et al. An evaluation of the factors associated with statin dose management and low-density lipoprotein-cholesterol goal attainment. Dis Manag Health Outcomes 14:32–44, 2006.
23. National Institutes of Health. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI), Bethesda, MD, 2007.
24. Bender B, Milgrom H, and Rand C. Nonadherence in asthmatic patients: Is there a solution to the problem? Ann Allergy Asthma Immunol 79:177–185, quiz 185–176, 1997.
25. Milgrom H, Bender B, Ackerson L, et al. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 98:1051–1057, 1996.
26. Schmaling KB, Afari N, and Blume AW. Predictors of treatment adherence among asthma patients in the emergency department. J Asthma 35:631–636, 1998.
27. Bender BG, Pedan A, and Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. J Allergy Clin Immunol 118:899–904, 2006.
28. Schwartzman S, and Morgan GJ Jr. Does route of administration affect the outcome of TNF antagonist therapy? Arthritis Res Ther 6(suppl 2):S19–S23, 2004.
29. Conway B, Prasad J, Reynolds R, et al. Directly observed therapy for the management of HIV-infected patients in a methadone program. Clin Infect Dis 38(suppl 5):S402–S408, 2004.
30. Garner P, Smith H, Munro S, and Volmink J. Promoting adherence to tuberculosis treatment. Bull World Health Organ 85: 404–406, 2007.
31. DiMatteo MR. Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. Med Care 42:200–209, 2004.
32. Haynes RB, Yao X, Degani A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2005, Issue 4. Art no. CD000011.pub2. DOI 10.1002/14651858.CD000011.pub2.
33. Horne R. Compliance, adherence, and concordance: Implications for asthma treatment. Chest 130(suppl 1):65S–72S, 2006. □