Primary Adherence to Controller Medications for Asthma Is Poor

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Abstract

Rationale: Few previous studies have evaluated primary adherence (whether a new prescription is filled within 30 d) to controller medications in individuals with persistent asthma.

Objective: To compare adherence to the major controller medication regimens for asthma.

Methods: This was a retrospective cohort study of enrollees from five large health plans. We used electronic medical data on patients of all ages with asthma who had experienced an asthma-related exacerbation in the prior 12 months. We studied adherence measures including proportion of days covered and primary adherence (first prescription filled within 30 d).

Measurements and Main Results: Our population included 69,652 subjects who had probable persistent asthma and were prescribed inhaled corticosteroids (ICSs), leukotriene antagonists (LTRAs), or ICS/long-acting β-agonists (ICS/LABAs). The mean age was 37 years and 58% were female. We found that 14–20% of subjects who were prescribed controller medicines for the first time did not fill their prescriptions. The mean proportion of days covered was 19% for ICS, 30% for LTRA, and 25% for ICS/LABA over 12 months. Using multivariate logistic regression, subjects prescribed LTRA were less likely to be primary adherent than subjects prescribed ICS (odds ratio, 0.82; 95% confidence interval, 0.74–0.92) or ICS/LABA (odds ratio, 0.88; 95% confidence interval, 0.80–0.97). Black and Latino patients were less likely to fill the prescription compared with white patients.

Conclusions: Adherence to controller medications for asthma is poor. In this insured population, primary adherence to ICSs was better than to LTRAs and ICS/LABAs. Adherence as measured by proportion of days covered was better for LTRAs and ICS/LABAs than for ICSs.

Keywords: asthma; adherence; medications; inhaled corticosteroids; leukotriene antagonists

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Asthma affects up to 300 million people in the world and 25.9 million people in the United States (1). Inhaled corticosteroids (ICSs) improve lung function, decrease the number of asthma-related hospitalizations, reduce emergency department (ED) visits, and limit the use of oral corticosteroids (2–5). Evidence-based guidelines recommend that ICSs should be the preferred first-line therapy for patients with persistent asthma, with leukotriene antagonists (LTRAs) as an alternate or add-on medication (6). National guidelines recommend the use of combination inhaled corticosteroid/long-acting β-agonists (ICS/LABAs) if asthma is uncontrolled with ICSs and/or LTRAs (6). Nevertheless, severe asthma exacerbations persist despite efficacious controller medicines. In 2011, more than half of Americans who had asthma experienced exacerbations (7).

Underuse of controller medications for asthma is common and contributes to severe exacerbations, including hospitalizations

and emergency department visits (8). Underuse of controller medications may be due to provider underdiagnosis or undertreatment of asthma, or patient medication nonadherence (9). Poor adherence to ICSs has been estimated to account for up to 60% of asthma-related hospitalizations (10–14). Furthermore, it has been suggested that optimal asthma control entails adherence rates to medication treatment more than 75% of the time (15). To date, studies of adherence to asthma controller medications in real-world populations have focused on dispensing data. To our knowledge, few studies have linked prescription and dispensing data to address primary nonadherence (i.e., when a provider prescribes a medication but the patient does not fill it) to controller medications for asthma. The objective of this study was to compare real-world adherence, including both primary and secondary adherence, to the major controller regimens (ICSs, LTRAs, and ICS/LABAs) in diverse, insured populations.

Methods

Study Design

This was a retrospective cohort study of individuals with asthma in the Population-Based Effectiveness in Asthma and Lung Diseases (PEAL) Network. The network includes data from five health plans: Harvard Pilgrim Health Care (HPHC), HealthPartners (HP), Kaiser Permanente Northern California (KPNC), Kaiser Permanente Georgia (KPGA), and Kaiser Permanente Northwest (KPNW). KPNC, KPGA, and KPNW are closed systems. The institutional review board at each site approved this study. Electronic medical record data from enrollees from each of the five sites were pooled to form the PEAL Data Warehouse, which includes information on subject demographics, enrollment type, prescriptions of medications, dispensings of medications, health care resource use, and smoking status.

Setting and Participants

Subjects of all ages were identified from claims records and electronic medical records. Subjects were potentially eligible for the PEAL asthma population if they had any discharge diagnosis for asthma based on the International Classification of Diseases, Ninth Revision (ICD-9) code for asthma (493.xx) during an acute inpatient hospital stay, ED visit, ambulatory visit, or nonacute institutional stay during the period of January 1, 2004 to December 31, 2010. This time window varied for each site by up to 1 year, based on data availability. The exact time windows were as follows: January 1, 2004–December 31, 2010 for HP, HPHC, and KPNW; January 1, 2004–August 31, 2010 for KPNC, and January 1, 2005–December 31, 2010 for KPGA.

Next, we identified subjects who had probable persistent asthma in the baseline period, which we defined as having at least one eligible health care encounter (hospitalization, ED visit, or dispensing of oral corticosteroids of 3 d or more) and continuous enrollment during the 12-month period before the order for an ICS, LTRA, or ICS/LABA was written. Orders for individual ICS and LABA inhalers on the same day or combination ICS/LABA inhalers were included in the ICS/LABA group. We conducted our analyses on an episode level rather than a patient level because we hypothesized that the same person can have different adherence patterns toward different controller medications.

For this study, we focused our results on new episodes where the subject who received the controller medication did not receive any other controller medications in the past 365 days. The goal of this restriction was to identify subjects who were more likely to be receiving their first controller medication prescription. We did not include subjects who switched to or added other controller medications. Our rationale was that new initiators might have different adherence compared with subjects who were switching from a previous controller medication. We also excluded subjects who were not continuously enrolled in the respective health plan for the 365 days after the first controller medication prescription.

Adherence Measures

Whereas previous studies have focused on using medication dispensing data as surrogate measures of adherence, we combined electronic data on prescriptions from providers and fills to determine a more accurate measure of adherence. For each of the three major controller medications (ICS, LTRA, combination ICS/LABA), we studied four measures of medication adherence. First, we measured primary adherence, defined as whether the first prescription was filled within 30 days. Second, we studied early-stage persistence, defined as a prescription that was filled within 30 days and again between 31 and 180 days after the prescription was provided. Subjects who met criteria for primary nonadherence were not considered to be early-stage nonpersistent. Third, rather than measure the proportion of days covered (PDC), calculated by dividing days supplied by the days in the time period of interest, which uses an index date based on the first dispensing, we calculated an adjusted PDC, which used an index date based on the date of the first prescription rather than the date of the fill (16). The PDC analyses limited each person to a fixed interval of 365 days. We stratified adjusted PDC by less than 75% and by 75% or more, based on a prior study (17).

Statistical Analysis

We evaluated the following variables that might influence adherence. These variables included age; sex; race; asthma-related ED visits, hospitalizations, and outpatient visits in the 365 days before initial fill of controller medication; and dispensings of oral corticosteroids or short-acting β-agonists in the 365 days before initial fill of the controller medication. In addition, we evaluated the following predictor variables: modified Charlson score, which included all diseases that comprise the Charlson Comorbidity Index except chronic pulmonary disease because it includes the diagnosis of asthma; number of medications in the prior 365 days (counted by generic names) because it has been demonstrated to account for comorbidity (18); and history of additional comorbid illnesses, which included allergic rhinitis, gastroesophageal reflux disease, and acute respiratory infection (19). We stratified our results by controller medication group (ICS, LTRA, ICS/LABA).

Because adherence may be different for subjects who have other comorbid chronic illnesses besides asthma, for sensitivity analyses we conducted stratified analyses of subjects who had other comorbid illnesses versus subjects who had no other comorbid illnesses. The results of the stratified analyses were similar to those of the combined analysis; thus, we present only the combined results here. The comorbid illnesses were diagnosed by ICD-9 codes, used in prior studies, and included cystic

fibrosis (277.00–277.02), immunodeficiency (279.xx), bronchiectasis (494.0–494.1), hereditary and degenerative diseases of the central nervous system (330–337.xx), psychoses (290–301.xx), mental retardation (317, 318.0–318.2, 319), congestive heart failure (428–429.9), chronic bronchitis, emphysema (490.xx, 491.20–492.8), pulmonary hypertension, pulmonary embolism (415.11–415.19, 416.0–416.8, 417.xx), and chronic obstructive pulmonary disease (496.xx) (20).

Results

Study Population

We identified a population of 614,056 subjects who had one or more asthma diagnoses and were prescribed at least one controller medication (ICS, ICS/LABA, LTRA), accounting for 2,535,069 prescriptions. We then limited our population to the 91,003 subjects who experienced an asthma-related hospitalization, ED visit, or use of oral corticosteroids for 3 days or more. Of the 91,003 subjects with probable persistent asthma, 77% (69,652) had not received a controller medication in the prior 12 months. Our population included 69,652 subjects with probable persistent asthma who received a controller medication for the first time in 12 months: 92% were prescribed an ICS (63,998); 5%, an LTRA (2,197); and 3%, an ICS/LABA (2,197). The mean age was 37 years, and 58% (40,153) were female. Baseline demographics stratified by controller medication are presented in Table 1. Because the results of the analyses of the subgroups of subjects who had other chronic conditions in addition to asthma and who did not have other chronic conditions were similar, we combined all of the groups.

Table 1. Demographics at baseline*

	n = 69,652		
	ICS (*n = 63,998*)	ICS/LABA (*n = 3,457*)	LTRA (*n = 2,197*)
HMO			
HPHC	2% (1,384)	11% (381)	4% (83)
HP	3% (1,719)	17% (583)	10% (223)
KPNC	74% (47,120)	49% (1,692)	65% (1,426)
KPNW	14% (9,111)	14% (501)	12% (253)
KPGA	7% (4,664)	9% (300)	10% (212)
Race			
Asian	9% (5,460)	5% (182)	7% (153)
Black	11% (6,792)	11% (371)	9% (208)
Latino	15% (9,622)	8% (273)	11% (250)
White	48% (30,616)	60% (2,065)	52% (1,150)
Missing	18% (11,508)	16% (566)	20% (436)
Sex			
Female	57% (36,685)	63% (2,172)	59% (1,296)
Age on prescription date			
0–12 yr	28% (17,914)	3% (103)	29% (642)
13–17 yr	7% (4,476)	4% (134)	8% (177)
18–35 yr	13% (8,258)	13% (461)	16% (343)
36–64 yr	39% (24,765)	54% (1,874)	38% (844)
65+ ερ	13% (8,585)	26% (885)	9% (191)
Charlson score ⩾1	17% (10,712)	31% (1,087)	11% (236)
History of allergic rhinitis†	13% (8,538)	16% (559)	32% (701)
History of acute respiratory illness†	50% (32,035)	50% (1,714)	54% (1,177)
History of gastroesophageal reflux disease†	10% (6,439)	19% (655)	10% (219)
History of hospitalization†	4% (2,705)	9% (299)	4% (83)
History of ED visit†	12% (7,909)	13% (456)	11% (235)
History of OCS use†	94% (60,259)	94% (3,245)	95% (2,093)
Number of prescriptions for SABA†			
0	17% (11,001)	26% (901)	32% (704)
1–5	80% (51,038)	64% (2,227)	64% (1,415)
6+	3% (1,959)	10% (329)	4% (78)

Definition of abbreviations: ED = emergency department; HMO = health maintenance organization; HPHC = Harvard Pilgrim Health Care; HP = HealthPartners; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid/long-acting β-agonist; KPGA = Kaiser Permanente Georgia; KPNC = Kaiser Permanente Northern California; KPNW = Kaiser Permanente Northwest; LTRA = leukotriene antagonist; OCS = oral corticosteroid; SABA = short-acting β-agonist.
*Index date is date of prescription.
†In previous 365 days.

Bivariate Analyses

Bivariate results of adherence measures are shown in Table 2. In these subjects—who were not prescribed any other controller medications in the prior year—primary adherence was greatest in those prescribed ICSs: 86% prescribed an ICS filled the prescription within 30 days; 82%, ICS/LABA; and 80%, LTRA ($P < 0.0001$ for ICS/LABA vs. ICS; $P < 0.0001$ for LTRA vs. ICS). In contrast, early-stage persistence was highest for subjects taking LTRAs, as 64% prescribed ICSs filled within 30 days and again between 31 and 180 days after the prescription was provided; 60%, ICS/LABA; and 76%, LTRA ($P < 0.0001$ for ICS/LABA vs. ICS; $P < 0.0001$ for LTRA vs. ICS). The mean adjusted PDC was 21% for ICS; 25%, ICS/LABA; and 30%, LTRA.

Multivariate Analyses

Using multivariate logistic regression analysis (Table 3), we found that subjects prescribed LTRA were less likely to be primary adherent than subjects prescribed ICS (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.74–0.92), as were subjects prescribed ICS/LABA (OR, 0.88; 95% CI, 0.80–0.97). Subjects prescribed LTRA were more likely to be early-stage persistent than subjects prescribed ICS (OR, 1.82; 95% CI, 1.64–2.04). Subjects prescribed LTRA or ICS/LABA were more likely to be adherent as measured by adjusted PDC equal to or greater than 75% than subjects prescribed ICS (OR, 6.21 [95% CI, 5.41–7.19] and 2.13 [95% CI, 1.82–2.48], respectively).

Table 4 shows the predictors of two of the adherence measures: primary adherence and adjusted PDC equal to or greater than 75%. Black and Latino subjects were less likely to be primary adherent (OR, 0.77 [95% CI, 0.71–0.83] and OR, 0.86 [95% CI, 0.81–0.92]), whereas Asian subjects were more likely to be primary adherent (OR, 1.14 [95% CI, 1.04–1.25]) compared with white subjects. Subjects who had a history of hospitalization or need for oral corticosteroids in the prior 365 days were

Table 2. Outcomes by new episodes for subjects with probable persistent asthma who were prescribed no other controller medications in the prior 365 days

	n = 69,652			ICS/LABA vs. ICS	LTRA vs. ICS
	ICS (*n = 63,998*)	ICS/LABA (*n = 3,457*)	LTRA (*n = 2,197*)		
Primary adherence	86% (54,731)	82% (2,836)	80% (1,755)	$P < 0.0001$	$P < 0.0001$
Early-stage persistence	64% (40,842)	60% (2,091)	76% (1,661)	$P < 0.0001$	$P < 0.0001$
Adjusted PDC > 75%	3% (1,748)	7% (239)	13% (282)	$P < 0.0001$	$P < 0.0001$
Mean adjusted PDC	21% (19%)	25% (27%)	30% (32%)	$P < 0.0001$	$P < 0.0001$

Definition of abbreviations: ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid/long-acting β-agonist; LTRA = leukotriene antagonist; PDC = proportion of days covered.

more likely to be primary adherent (OR, 1.24 [95% CI, 1.11–1.39] and OR, 1.56 [95% CI, 1.41–1.73]). Subjects with a prior history of hospitalization or ED visit in the previous 365 days were more likely to have adjusted PDC equal to or greater than 75%.

Discussion

Our study had three key findings. First, many patients with asthma are not taking controller medications as prescribed. Second, long-term adherence to LTRAs and ICS/LABAs is better than to ICSs; however, among patients receiving a controller medication for the first time, primary adherence is better to ICSs than to LTRAs or ICS/LABAs. Third, Latino and black patients are less likely to be adherent to controller medications for asthma.

We found that adherence to controller medications for asthma was low across all adherence measures, as we found that 14–20% of subjects who were prescribed controller medicines for the first time did not fill their prescriptions. A prior study by Fischer and colleagues that linked electronic prescriptions and fills to study primary adherence found similar low rates of primary adherence. However, Fischer and colleagues included rescue medications in the medications for asthma, and it is plausible that some of these patients who received an electronic prescription did not need the medication and thus did not fill it (9). Another study by Liberman and colleagues studied fills after a prescription for an asthma controller medication and found that 20% of prescriptions were unfilled at 60 days. The study by Liberman and colleagues did not limit the study to subjects with asthma; thus, it is plausible that some of the subjects who received a controller medication for asthma did not have asthma and did not need the controller medication (21). Furthermore, Liberman and colleagues did not compare adherence to the various classes of controller medications. Our study is unique in that we focused on patients who had probable persistent asthma and who most likely needed the prescribed controller medicine. Our finding of low primary adherence to controller medications in patients with probable persistent asthma supports the need for interventions such as follow-up office visits, phone calls, text messages, and use of electronic medical records and their automatic features to trigger physician and patient alerts of a failure to fill medications (22). Addressing concerns on the importance of controller medications for asthma may be particularly important for Latino and black patients.

In subjects who filled their prescription at least once, the adjusted PDC for ICSs was low. The adjusted PDC of 19% was similar to previous studies that have reported traditional PDC for ICSs ranging from 15 to 24%, yet the PDC was still low (23, 24). The traditional PDC is more commonly used because many administrative data sets lack prescription data; however, a limitation is that these estimates of PDC do not account for individuals who never filled their ICS prescription. Our finding that adherence to LTRAs and ICS/LABAs is better than adherence to ICSs is supported by previous studies. A study by Maspero and colleagues found that adherence to montelukast, an LTRA that is administered orally, is greater than to inhaled beclomethasone, an ICS, and children and parents reported that montelukast was more convenient and less difficult to use (25). Another study that examined prescription refills found that adherence to montelukast was significantly greater than to an ICS (26). A clinical trial by Perrin and colleagues found that adherence to ICS/LABAs was better than to ICSs, and one potential reason was that the addition of a bronchodilator (LABA) provides the patient with immediate symptomatic benefit and could therefore be taken more regularly compared with an ICS, which does not provide such an immediate benefit (27). Interestingly, our study suggests that primary adherence to ICSs was better than to LTRAs or ICS/LABAs for new initiators of controller medications.

Table 3. Odds of medication adherence outcomes by asthma controller medication class

	OR (CI)	
	LTRA vs. ICS	ICS/LABA vs. ICS
Primary adherence	0.82 (0.74–0.92)	0.88 (0.80–0.97)
Early-stage persistence	1.82 (1.64–2.04)	0.96 (0.88–1.04)
Adjusted PDC ⩾ 75%	6.21 (5.41–7.19)	2.13 (1.82–2.48)

Definition of abbreviations: CI = confidence interval; ICS = inhaled corticosteroid; ICS/LABA = inhaled corticosteroid/long-acting β-agonist; LTRA = leukotriene antagonist; OR = odds ratio; PDC = proportion of days covered.

Table 4. Predictors influencing primary adherence and adjusted proportion of days covered*

	Primary Adherence	Adjusted PDC > 75%
LTRA vs. ICS	0.82 (0.73–0.92)	6.29 (5.43–7.25)
ICS/LABA vs. ICS	0.88 (0.80–0.97)	2.18 (1.88–2.54)
Race		
Black vs. white	0.77 (0.71–0.83)	0.57 (0.48–0.67)
Latino vs. white	0.86 (0.81–0.92)	0.61 (0.52–0.71)
Asian vs. white	1.14 (1.04–1.25)	0.84 (0.71–0.99)
Female vs. male	0.99 (0.95–1.04)	0.88 (0.81–0.97))
Age		
0–12 yr vs. ⩾65 yr	0.99 (0.90–1.08)	0.89 (0.76–1.05)
13–17 yr vs. ⩾65 yr	0.85 (0.75–0.95)	0.24 (0.18–0.33)
18–35 yr vs. ⩾65 yr	0.77 (0.70–0.84)	0.24 (0.19–0.30)
36–64 yr vs. ⩾65 yr	1.00 (0.93–1.07)	0.61 (0.54–0.69)
History of hospitalization†	1.24 (1.11–1.39)	1.55 (1.31–1.83)
History of ED visit†	0.91 (0.84–0.98)	1.29 (1.12–1.47)
History of OCS†	1.56 (1.41–1.73)	1.13 (0.92–1.39)

Definition of abbreviations: ED = emergency department; ICS = inhaled corticosteroids; ICS/LABA = inhaled corticosteroid/long-acting β-agonists; LTRA = leukotriene antagonist; OCS = oral corticosteroid; PDC = proportion of days covered.
*All models controlled for age, sex, race, asthma-related ED visits, hospitalizations, and outpatient visits in the 365 days prior; and dispensings of oral corticosteroids or short-acting β-agonists in the 365 days prior. We evaluated the following predictor variables: modified Charlson Comorbidity Index, number of medications in the prior 365 days (counted by generic names), history of allergic rhinitis, gastroesophageal reflux disease, and acute respiratory infection.
†In the previous 365 days.

Strengths of our study include a large, real-world, diverse population and the availability of both prescription and dispensing data. Most previous studies of adherence focus on dispensing data alone or are conducted in the setting of a randomized clinical trial. This is one of the first studies, to our knowledge, that focuses on adherence in individuals with probable persistent asthma who most likely benefit from controller medications. Despite these strengths, several caveats deserve mention. First, residual confounding by indication, despite our efforts to minimize confounding, may contribute to our findings. For example, it is plausible that adherence to ICS/LABAs was higher because those patients had more severe asthma and thus were more likely to need the ICS/LABAs. Nevertheless, this would not explain why adherence to LTRAs was also better than adherence to ICS/LABAs. It is possible that patients were given samples for LTRAs or were instructed to try over-the-counter allergy medications, which may explain their poor primary adherence compared with ICS but better adjusted PDC compared with ICS. In addition, our measures of adherence are based on electronic data and do not capture whether individuals were taking their dispensed medications or administering them properly. These types of adherence measures, however, have been associated with clinical outcomes in other studies. Furthermore, we only assessed adherence related to filling the prescription. We were unable to be certain that patients took the medications or used the inhalers correctly. In addition, our study was unable to answer why patients are nonadherent. For example, we were unable to assess whether subjects were more adherent to LTRAs because the medication was easier to take than inhalers. Moreover, some individuals included in our study did not have a short-acting β-agonist (SABA) prescription in the previous 365 days, which may suggest to some that the individuals did not have asthma and did not fill their controller medications because they were not needed. However, we conducted our analyses while excluding subjects without SABA use, and our results were similar. Thus, we believe our study population does represent a population of subjects with asthma. An additional limitation concerns our results for subjects ages 65 years and older, who may not be representative of a general population at this age because our population included subjects who were still covered by private insurance rather than Medicare.

In conclusion, adherence to controller medications is poor. Many patients do not ever fill prescriptions for controller medications. When choosing controller medications for asthma, providers should address the importance of filling the first prescription and the need for persistent adherence. ■

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