Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma

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Background: Regular use of inhaled corticosteroids (ICSs) can improve asthma symptoms and prevent exacerbations. However, overall adherence is poor among patients with asthma.
Objective: To estimate the proportion of poor asthma-related outcomes attributable to ICS nonadherence.
Methods: We retrospectively identified 405 adults age 18 to 50 years who had asthma and were members of a large health maintenance organization in southeast Michigan between January 1, 1999, and December 31, 2001. Adherence indices were calculated by using medical records and pharmacy claims. The main outcomes were the number of asthma-related outpatient visits, emergency department visits, and hospitalizations, as well as the frequency of oral steroid use.
Results: Overall adherence to ICS was approximately 50%. Adherence to ICS was significantly and negatively correlated with the number of emergency department visits (correlation coefficient [*R*] = −0.159), the number of fills of an oral steroid (*R* = −0.179), and the total days' supply of oral steroid (*R* = −0.154). After adjusting for potential confounders, including the prescribed amount of ICS, each 25% increase in the proportion of time without ICS medication resulted in a doubling of the rate of asthma-related hospitalization (relative rate, 2.01; 95% CI, 1.06-3.79). During the study period, there were 80 asthma-related hospitalizations; an estimated 32 hospitalizations would have occurred were there no gaps in medication use (60% reduction).
Conclusions: Adherence to ICS is poor among adult patients with asthma and is correlated with several poor asthma-related outcomes. Less than perfect adherence to ICS appears to account for the majority of asthma-related hospitalizations.
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Key words: *Adherence, asthma, attributable risk, hospitalizations, inhaled corticosteroids, emergency department visits*

Abbreviations used
BHR: Bronchial hyperreactivity
CMA: Continuous, multiple-interval measure of medication availability
CMG: Continuous, multiple-interval measure of medication gaps
ED: Emergency department
HMO: Health maintenance organization
ICS: Inhaled corticosteroid
RR: Relative rate

In 2001, an estimated 31.1 million adults in the United States had a diagnosis of asthma.[1] Asthma is a leading cause of preventable hospitalizations, and it accounts for an estimated 14 million days of missed school and 100 million days of restricted activity yearly.[1] It has been estimated that regular use of inhaled corticosteroids (ICSs) could reduce asthma hospitalizations by as much as 80%,[2] and that the risk of death from asthma decreases by 21% for each additional ICS canister used.[3] Despite such potential, patients with asthma appear to adhere poorly to prescribed ICS medications. For example, Cochrane et al[4] found that patients with asthma took their ICS as directed on only 20% to 73% of days. On 24% to 69% of days, patients took <50% of the prescribed dose.

Although routine use of ICS can markedly improve symptoms and reduce asthma complications,[5-7] the contribution of medication nonadherence to poor asthma control has not been established. Therefore, the objective of this study was to measure the association between adherence to ICS and the frequency of asthma-related outpatient visits, emergency department (ED) visits, hospitalizations, and oral steroid use.

METHODS

This study was approved by the Institutional Review Board and was in compliance with its Health Insurance Portability and Accountability Act policy. Patients were all members of a large health maintenance organization (HMO) in southeast Michigan, and they received their care from a large, multispecialty medical group consisting of approximately 800 physicians. Medical care claims data

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TABLE I. Characteristics of adults age 18 to 50 years with asthma by the availability of adherence information, 2000 to 2001

Characteristic	Total (n = 405)	Patients with adherence information (n = 176)	Patients without adherence information (n = 229)	*P*-value*
Age, y ± SD†	38.3 ± 8.8	40.4 ± 7.9	36.6 ± 9.1	.001
Female (%)	270 (66.7)	119 (67.6)	151 (65.9)	.751
Race				.304
African American (%)	192 (47.4)	75 (42.6)	117 (51.1)	
White (%)	200 (49.4)	94 (53.4)	106 (46.3)	
Other (%)	13 (3.2)	7 (4.0)	6 (2.6)	
Medication use in 2000-2001				
≥1 ICS fill (%)	231 (57.0)	176 (100.0)	55 (24.0)	.001
Mean ICS fills per person (±SD)	3.5 ± 5.3	7.6 ± 5.8	0.3 ± 0.8	.001
≥1 inhaled β-agonist fill (%)	281 (69.4)	168 (95.5)	113 (49.3)	.001
Mean inhaled β-agonist fills per person (±SD)	7.4 ± 9.6	13.5 ± 10.8	2.6 ± 4.7	.001
≥1 oral corticosteroid fill (%)	183 (45.2)	118 (67.1)	65 (28.4)	.001
Mean oral corticosteroid fills per person (±SD)	1.5 ± 2.9	2.6 ± 3.7	0.7 ± 1.8	.001
Medical encounters in 2000-2001				
≥1 ED visit for asthma (%)	101 (24.9)	49 (27.8)	52 (22.7)	.248
Mean ED visits for asthma per person (±SD)	0.5 ± 1.2	0.6 ± 1.5	0.4 ± 1.1	.151
≥1 hospitalization for asthma (%)	38 (9.4)	23 (13.1)	15 (6.6)	.038
Mean hospitalizations for asthma per person (±SD)	0.2 ± 0.8	0.3 ± 1.1	0.1 ± 0.4	.022
≥4 outpatient visits for asthma (%)	145 (35.8)	104 (59.1)	41 (17.9)	.001
Mean outpatient visits for asthma per person (±SD)	3.8 ± 5.2	6.2 ± 6.3	2.0 ± 3.2	.001

*For the comparison of those with adherence information to those without such information.
†Age on January 1, 1999.

were used retrospectively to identify individuals with asthma. Individuals age 18 to 50 years with 1 or more of the following in the index year (January 1, 1999, to December 31, 1999) were considered to have asthma: (1) 1 or more hospitalizations with the primary discharge diagnosis of asthma, (2) 1 or more ED visits with the primary diagnosis of asthma, or (3) 4 or more outpatient visits with asthma as a diagnosis. These criteria were adapted from claims-based measures of asthma that have been reported elsewhere.[8-10] To examine the relationship between medication adherence and outcomes among adult patients with asthma, data had to be available for the 2 years after the index year. Therefore, to be included in the analyses, patients with asthma had to be continuously enrolled in the HMO between January 1, 1999, and December 31, 2001; have both medical and pharmacy benefit coverage during this time; and have their care provided by physicians in the medical group. Patients were excluded if they had a diagnosis of chronic obstructive pulmonary disease or congestive heart failure at any outpatient visit, ED visit, or hospitalization between January 1, 1999, and December 31, 2001.

The medical records of all individuals fulfilling these criteria for asthma were abstracted for ICS use and dosage information. Abstracted information was recorded and entered into an electronic database by using TELEform (Cardiff Software, Vista, Calif) by accredited medical record abstractors. These data were then linked with prescription fill information from pharmacy claims data. The number of days that a given fill of an ICS would last (ie, days supplied) was calculated by dividing the canister size (ie, puffs per canister) as derived from National Drug Codes in pharmacy claims by the dosage information (ie, puffs per day) obtained in medical records. The calculated days' supply was used to estimate 2 measures of adherence: (1) continuous, multiple-interval measure of medication availability (CMA), and (2) continuous, multiple-interval measure of medication gaps (CMG). The calculation of these indices is discussed in detail by Steiner and Prochazka.[11] Briefly, CMA is cumulative days' supply/total number of days between refills during the observation period, and CMG is total days of treatment gaps/total number of days between refills during the observation period.[11] Although complementary, CMG indices assess the effect of lapses in therapy (increases with increasing gaps or delays in refills), whereas CMA indices assess the effect of cumulative drug dosage (increases with increasing frequency of prescription fills).[11,12] These 2 indices were calculated for each patient beginning with the first fill of an ICS and ending with the last fill within the period of January 1, 2000, through December 31, 2001. Therefore, ICS adherence could be calculated only for individuals with at least 2 fills of an ICS in the 2-year observation period (n = 176). These calculations accounted for changes in dosage and type of ICS. To ensure that gaps in ICS refills were not a result of clinicians stopping medication, we also abstracted provider notes for encounters in which an ICS was explicitly stopped and another ICS was not started. Among patients for whom adherence could be measured, we identified only 1 patient who had ICS stopped while adherence was being measured and another ICS was not started contemporaneously. Inclusion or exclusion of this patient did not materially change the results; this individual was included in all analyses.

Statistical analysis

Adherence indices were calculated as previously described. Subjects for whom adherence could be calculated were compared with individuals for whom adherence could not be calculated. Differences in characteristics were assessed by using a χ^2 test for

TABLE II. Correlation between measures of adherence to ICSs and asthma-related outcomes in adult patients with asthma, 2000 to 2001

Variable 1	Variable 2	Correlation
CMA	Asthma-related outpatient visits	−0.015
	Asthma-related ED visits	−0.159*
	Asthma-related hospitalizations	−0.130
	Fills of oral steroids	−0.179*
	Days of oral steroids	−0.154*
CMG	Asthma-related outpatient visits	0.030
	Asthma-related ED visits	0.171*
	Asthma-related hospitalizations	0.147
	Fills of oral steroids	0.190*
	Days of oral steroids	0.164*

CMA denotes continuous, multiple interval of medication availability which is equal to the cumulative days' supply of inhaled steroids divided by the total number of days between refills for the period January 1, 2000 through December 31, 2001.
CMG denotes continuous, multiple-interval measures of medication gaps which, on the basis of days' supply of inhaled steroids, is equal to the total number of days of without an inhaled steroid divided by the total days between refills for the period January 1, 2000 through December 31, 2001.
*$P < .05$.

categorical variables and a nonparametric Mann-Whitney 2-sample test for continuous variables.

The primary outcome measures were the number of asthma-related outpatient visits, asthma-related ED visits, asthma-related hospitalizations, and oral steroid uses during the period of January 1, 2000, through December 31, 2001. The outcome measures were related to CMA and CMG by using a Spearman correlation coefficient. Poisson regression methodology was then used to assess the relationship between adherence indices and the frequency of asthma-related outcomes.[13] A univariable model was fit, followed by 2 multivariable models. Multivariable models adjusted for potential confounders including potential markers of disease severity, such as the number of β-agonist fills,[8] the number of ICS fills, and the prescribed number of ICS fills. The first multivariable model (model 1) adjusted for sex, race, age, number of β-agonist fills, and number of ICS fills (log-transformed). The second multivariable model (model 2) replaced the number of ICS fills with prescribed number of ICS fills. This last variable was computed as the number of ICS fills divided by CMA (log-transformed). The model was fit with a correction for overdispersion. A relative rate (RR) was estimated in each model for a 0.25 change in either CMA or CMG.

We adapted the methodology of Greenland and Drescher[14] to calculate the proportion of hospitalizations attributable to nonadherence. The coefficient estimates from the multivariable Poisson model (model 2) were used to derive an asthma-related hospitalization rate for each individual with adherence information (n = 176) under conditions of perfect ICS adherence (ie, CMG set to 0). This approach allowed us to account for other individual risk factors that could contribute to the rate of hospitalization. The expected number of asthma-related hospitalizations among persons with adherence information was therefore the sum of these individual rates. The number of asthma-related hospitalizations attributable to nonadherence was then calculated by subtracting the expected number of asthma-related hospitalizations from the observed number of hospitalizations among patients with adherence information. The proportion of all asthma-related hospitalizations attributable to nonadherence was estimated by dividing this difference by the total number of asthma-related hospitalizations observed among the 405 adults studied (ie, persons with and without adherence information). This calculation assumes that the only hospitalizations that could have been prevented by improved adherence were among the 176 subjects for whom adherence was measured. The asthma-related hospitalizations that occurred in the 229 (56%) patients without adherence information were considered immutable and therefore contributed only to the calculation of the denominator, the total asthma-related hospitalizations, but not to the numerator, the number of asthma-related hospitalizations preventable by improved adherence. Statistical analyses were performed by using SAS v8.0 (SAS Institute, Cary, NC).[15]

RESULTS

In the year 1999, 2150 patients between the ages of 18 and 50 years met the study criteria for having asthma. Of these adult patients with asthma, 461 were continuously enrolled in the HMO; had both medical and pharmacy benefits; and had their care provided by a group physician between January 1, 1999, and December 31, 2001. Another 56 patients were excluded because they had a diagnosis of chronic obstructive pulmonary disease or congestive heart failure. The characteristics of the remaining 405 patients are shown in Table I. Approximately equal numbers were African American (n = 192) and white (n = 200). Two-hundred thirty-one (57.0%) patients had at least 1 ICS fill in either 2000 or 2001, whereas 281 (69.4%) had at least 1 prescription fill of an inhaled β-agonist. The adherence measures, CMA and CMG, could be calculated for 176 patients (ie, patients who had at least 2 fills of an ICS in the years 2000 and 2001). Not surprisingly, those for whom adherence could be measured had greater numbers of ICS fills compared with those for whom adherence could not be measured. The former also had other indicators of more severe asthma, such as greater use of β-agonist inhalers, greater use of oral corticosteroids, and more frequent asthma-related hospitalizations. The mean CMA and CMG for ICS were 0.50 (SD, ±0.37) and 0.54 (SD, ±0.27), respectively. In other words, overall adherence to ICS, as estimated by CMA or 1-CMG, was approximately 50%.

As expected, CMA, a measure that increases when patients fill their ICS prescriptions on time, was negatively associated with poor asthma outcomes (Table II). Similarly, CMG, which increases with increasing lapses or delays in filling prescriptions, was positively associated with poor asthma outcomes. Both CMA and CMG were significantly correlated with the number of asthma-related ED visits and the frequency of oral steroid use (both total number of prescriptions filled and total number of days treated). The weakest associations were seen for the frequency of outpatient asthma visits, which did not appear to be correlated with level of adherence. Slightly stronger correlations were seen between adherence and asthma outcomes when using CMG compared with CMA.

Because the relationships seen between adherence indices and asthma outcomes could be reflective of total ICS use rather than adherence alone, we simultaneously adjusted for inhaled steroid use, age, sex, race, and β-agonist in the regression models (Table III). In

TABLE III. Unadjusted and adjusted association between adherence and asthma-related outcomes in adults age 18 to 50 years, 2000 to 2001

	Per 25% increase in CMG		
Outcome	**Unadjusted RR (95% CI)**	**Model 1* RR (95% CI)**	**Model 2† RR (95% CI)**
Outpatient visit	1.07 (0.93-1.23)	1.13 (0.97-1.30)	0.96 (0.83-1.11)
Asthma-related ED visit	1.36 (0.97-1.92)	1.27 (0.85-1.77)	1.25 (0.84-1.85)
Asthma-related hospitalization	1.80 (1.04-3.14)‡	1.27 (0.75-2.14)	2.01 (1.06-3.79)‡
Fills of oral steroids	1.22 (0.99-1.50)	1.49 (1.10-2.02)‡	1.26 (0.95-1.67)
Days of oral steroids	1.18 (0.88-1.59)	1.53 (1.00-2.36)	1.27 (0.85-1.88)

*Adjusted for sex, race, age, number of β-agonist fills from 2000 to 2001, and number of ICS fills from 2000 to 2001.
†Adjusted for sex, race, age, number of β-agonist fills from 2000 to 2001, and prescribed number of ICS fills from 2000 to 2001 (ie, total number of ICS fills divided by CMA).
‡$P < .05$.

model 1, we adjusted for the total number of ICS fills made by individual patients in 2000 and 2001. Because the prescribed ICS dose may be a proxy for disease severity, in model 2, we adjusted by the total number of ICS fills that an individual should have had in 2000 and 2001 (ie, total number of ICS fills divided by CMA). As shown previously, nonadherence as measured by increasing CMG was positively, albeit not always significantly, associated with the rate of asthma-related ED visits, asthma-related hospitalizations, and oral steroid use in both the unadjusted and adjusted regression analyses. In the unadjusted model and in model 2, CMG was significantly associated with the rate of asthma-related hospitalizations. Each 25% increase in the proportion of time without ICS medication resulted in a doubling of the rate of asthma-related hospitalization (model 2, RR, 2.01; 95% CI, 1.06-3.79). CMG was also significantly associated with the rate of fills of an oral steroid (model 1, RR, 1.49; 95% CI, 1.10-2.02). Simultaneously adjusting models 1 and 2 for other potential markers of disease severity, such as oral steroid use and asthma-related hospitalizations, in 1999 did not substantively change our results (data not shown). CMA was similarly significantly associated with the rate of fills of an oral steroid (model 1, RR, 0.75; 95% CI, 0.58-0.97), meaning that each 25% increase in adherence to ICS as measured by CMA was associated in a 25% reduction in the rate of oral steroid fills (data not shown).

Between 2000 and 2001, there were 80 asthma-related hospitalizations among the 405 adults with asthma. Fifty-eight of asthma-related hospitalizations occurred among the 179 patients for whom adherence could be measured, and 22 hospitalizations occurred in those without adherence information. Among those for whom adherence could be measured, we estimate that the number of hospitalizations would have been reduced to 10.0 (82.8% reduction) were there no lapses in medication use (ie, CMG = 0). In other words, 60.0% of all asthma-related hospitalizations could be attributed to less than perfect adherence to ICS.

DISCUSSION

A previous study by Donahue et al[8] found that patients with asthma who filled a prescription for an ICS were 50% less likely to be hospitalized for asthma compared with patients who did not receive an inhaled steroid (relative risk, 0.5; 95% CI, 0.4-0.6). However, the investigators did not examine whether patients took their ICS as directed. We find that apart from the total number of ICS fills, gaps or lapses in adherence are an independent predictor of asthma-related hospitalizations. In fact, we estimate that 60% of all asthma-related hospitalizations in our study population could be attributed to less than perfect adherence to ICSs.

These findings comport with trials showing that cessation of ICSs can result in rapid declines in FEV_1, morning and evening peak expiratory flow, and quality of life, as well as increases in bronchial reactivity, daily asthma symptom scores, sputum eosinophils, and levels of exhaled nitric oxide.[16,17] For example, Haahtela et al[16] showed that average FEV_1 and bronchial hyper-reactivity (BHR) to methacholine did not change significantly in individuals switched from budesonide at 1200 μg per day to 400 μg per day, whereas switching to placebo resulted in a significant drop in FEV_1 and a rise in BHR. Vathenen et al[18] found that after 6 weeks of therapy with budesonide, BHR returned to baseline within a week of discontinuing treatment.

Although several studies have shown that overall patient adherence to ICS is poor,[4,19-21] few have examined the relationship between adherence and asthma outcomes. In a small study by Milgrom et al,[20] adherence to ICS was measured by using electronically monitored metered-dose inhalers in 24 asthmatic children age 8 to 12 years. During this 13-week study, children who required a burst dose of oral corticosteroids had a median ICS adherence value of 13.7%, compared with a median ICS adherence of 68.2% in children not requiring oral steroids ($P = .008$). In the current study, we have also found a significant correlation between the need for oral steroids and adherence to ICS. We did not, however, find a significant relationship between adherence and outpatient visits for asthma, which is not surprising, because the latter may not reflect poor asthma control.[22]

This study must be interpreted in light of its limitations. First, the study population examined here consisted of individuals with both medical and pharmaceutical coverage. On the basis of studies showing a positive

relationship between both commercial insurance possession and household income and adherence,[19,23] our estimates of overall adherence are likely to be greater than those of the general population. Similarly, our measurement of adherence was limited to persons with 2 or more fills of an ICS during the study period, and therefore, these estimates did not account for individuals who never filled their ICS prescription or filled it only once. Watts et al[24] performed a study of primary nonadherence (ie, the nonfilling of prescriptions) in Port Lincoln, South Australia. Of the 359 asthma medication prescriptions written, 108 (30%) were never filled in 6 months of follow-up. Together, these data suggest that the proportion of poor asthma outcomes attributable to nonadherence may be greater than reported here. When estimating the proportion of hospitalizations attributable to nonadherence, we adjusted for other risk factors that could have contributed to the rate of hospitalization. However, it is also possible that persons who were nonadherent differed from persons who were adherent in other unmeasured ways, which could have accounted for some of the difference in these rates. This may have resulted in an overestimation of the proportion of hospitalizations attributable to nonadherence. Before generalizing these results, it is also important to note that our definition of asthma may have identified patients with more severe asthma who were more likely to benefit from continuous ICS use. Because pharmacy claims data were used to measure adherence, we could not assess daily patterns of ICS use. Therefore, although CMG, a measure of gaps in ICS refills, was the better predictor of poor asthma outcomes, we could not distinguish protracted period off therapy from chronic or intermittent underdosing. This prevented us from being able to correlate specific patterns and timing of use with adverse asthma outcomes. Last, depending on the statistical method used, nonadherence to ICS was significantly associated with different poor asthma outcomes. However, the consistency of these associations in both magnitude and direction across outcomes suggests that statistical differences were a result of limited power rather than a true lack of association. Despite this limitation, nonadherence was still significantly associated with oral steroid use and asthma-related hospitalizations after adjusting for multiple potential confounders.

Although this study demonstrates the important relationship between ICS adherence and asthma-related outcomes, improving both is likely to be difficult. Bender et al[25] recently reviewed interventions to improve adherence among patients with asthma. The authors found that few behavioral or educational interventions were very effective at improving adherence and asthma control, despite considerable time investment in some cases. Similar disappointing results have been seen for adherence interventions in other disease conditions.[26]

However, recent data suggest that adherence can be improved when patients know that adherence is being measured and this information is regularly discussed with them. Onyirimba et al[27] measured adherence to ICS by using electronically monitored metered-dose inhalers in 19 patients with asthma over a 10-week period. Patients who received regular adherence feedback from their clinician had sustained levels of adherence >70% compared with those in the control group whose adherence rate fell below 30% by week 10. In a study by Reddel et al,[28] patients' overall adherence to peak expiratory flow measurement was 89% over a period of 72 weeks when participants were aware that peak expiratory flow meter use was being electronically recorded and these results were discussed with them regularly.

Our finding that ICS adherence, as measured by using both medical records and pharmacy claims data, is associated with important asthma outcomes suggests that these measures may be clinically useful. However, although medical records and pharmacy claims data are ubiquitous, patient adherence information is not, and to date, there are few studies looking at its introduction in clinical practice.[29,30] Developing a mechanism to feed back adherence information routinely to both clinicians and patients may result in improved adherence and better asthma control. Our demonstration that ICS adherence can be estimated by using prescription refill information, and that these measures are independently associated with important asthma outcomes, is a first step in that direction.

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