Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use

James L. Zazzali, Ph.D., M.P.H.,[1] Michael S. Broder, M.D., M.S.H.S.,[2] Theodore A. Omachi, M.D., M.B.A.,[1] Eunice Chang, Ph.D.,[2] Gordon H. Sun, M.D., M.S.,[2] and Karina Raimundo, B.Pharm., M.S.[1]

ABSTRACT

Background: *Oral corticosteroids (OCS) are a mainstay of asthma treatment. Their use increases the risk of various corticosteroid-related adverse events, but the extent of risk is poorly characterized.*

Objective: *To determine the incremental risk of possible corticosteroid-related adverse events (AE) in asthma among patients with high OCS use compared with patients who do not use OCS.*

Methods: *Patients with asthma in a commercial health care claims data base who were high-OCS users (≥30 days of OCS use annually) were matched to no-OCS users by age, sex, and geographic region, and the presence or absence of chronic obstructive pulmonary disease (COPD) as a comorbidity. We examined bone-related conditions, pneumonia, opportunistic infections, diabetes mellitus, and other disorders as potential AEs by using χ^2 tests to compare potential AE prevalence between the cohorts, with and without stratification by a COPD diagnosis. We controlled for the number of inhaled steroids (ICS) canisters filled.*

Results: *A total of 3604 patients with asthma and high OCS use were matched to 3604 patients who did not use OCS (mean age, 54.4; 68.1% female; 44.9% with COPD). Patients with high OCS use had statistically significantly higher rates of any potential AE compared with patients who did not use OCS (83.5% versus 78.1%), ($p < 0.001$). Rates of individual potential AEs were also higher in patients who used higher doses of OCS. Patterns of AEs were similar in patients with and those without COPD, with statistically significantly higher overall AE risk and individual risks in high-OCS users. The number of ICS canisters filled was not a significant predictor of AE.*

Conclusion: *Patients with asthma who were treated with OCS for ≥30 days per year have a greater overall risk of possible corticosteroid-related AEs compared with those patients with no OCS use, whether or not they had COPD.*

(Allergy Asthma Proc 36:268–274, 2015; doi: 10.2500/aap.2015.36.3863)

Oral corticosteroids (OCS) are a mainstay of treatment for severe asthma and are widely used to manage asthma exacerbations.[1] Although quite efficacious in controlling asthma, OCS use may also contribute to a variety of adverse events (AE), including bone fractures, diabetes mellitus, infections, hypertension, and cataracts.[2] Corticosteroid toxicity is believed to be associated with both average dosage and cumulative duration of use.[3] For example, the fracture risk increases within 3–6 months of OCS therapy initiation, and using more than 5 mg of prednisolone or equivalent daily appreciably reduces bone mineral density.[4] One study found that more than 90% of those who filled ≥60 days of OCS during an 18-month span subsequently reported at least one AE, most commonly weight gain.[5] Another study found that lipodystrophy, insomnia, and neuropsychiatric disorders were the most-frequent adverse events.[6]

Because of these risks, chronic OCS use is recommended only for patients with asthma whose disease cannot be controlled with both inhaled steroids (ICS) and long-acting β-agonists.[1] However, the incremental risks associated with OCS use across a broad range of known corticosteroid-related AEs have not been well elucidated, nor have specific levels of OCS use that confer excess risk been described.[3,7] Our objective was to determine the incremental risk of clinical adverse events commonly associated with steroids in patients with asthma and with high OCS use.

METHODS

Study Design and Data Source

This matched cohort study used U.S. commercial health care claims to examine the risk of possible corticosteroid AEs between patients with asthma and high use of OCS and those who did not use OCS. The claims data base is Health Insurance Portability and Account-

From [1]Genentech, Inc., South San Francisco, California, and [2]Partnership for Health Analytic Research, LLC, Beverly Hills, California
Presented as a poster at the American Thoracic Society 2014 International Conference, San Diego, California, May 16–21, 2014
This study was funded by Genentech, Inc.
J.L. Zazzali, T.A. Omachi, and K. Raimundo are employees of Genentech, Inc. M.S. Broder E. Chang, and G.H. Sun are employees of Partnership for Health Analytic Research, LLC, which was paid by Genentech, Inc. to conduct this research
Supplemental data available at www.IngentaConnect.com
Address correspondence to James L. Zazzali, Ph.D., Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990
E-mail address: zazzali.james@gene.com

ability Act compliant and includes ~15 million annual commercially insured lives from across the United States. The data base does not contain information on patient race or body mass index, nor does it contain protected health information. It was exempt from institutional review board review.

Study Population and Time Frame

A 2-year observation period (2008–2009) was used. By using a validated claims-based method for identifying patients with asthma, we included patients ≥18 years of age who had ≥2 medical claims with asthma as one of the listed diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification code 493.x) and had filled ≥2 asthma medications (Supplemental Appendix Tables 1 and 2) in 2008.[8] We excluded patients if they were not continuously enrolled during 2008–2009, or if they used any intravenous (IV) corticosteroids, because the dose of IV medications could not be determined with the source data base.

We classified identified patients with asthma into "high-OCS" and "no-OCS" groups. High-OCS use was defined as ≥30 days of supply in a year, regardless of cumulative dose. This definition was derived from previously published data by using a national cohort of 37,123 commercially insured patients with asthma, in which patients with ≥30 total annual days of supply were exposed to a median total cumulative annual dose of OCS of 1260 mg compared with 250 mg in those with <30 total annual days of supply (Table 1). The total prednisone equivalent dose increased in that study with each category of days supply, from 250 mg in patients with <30 annual days of supply group, to 965 mg in the 30–59 days of group, 1682 mg in the 30–89 days of group, and 2700 mg in those with ≥90 days of supply.[9]

To be categorized as high-OCS, the patients were required to be high-OCS users in both 2008 and 2009. Patients with low or intermediate OCS use used <30 days of supply of OCS in a year, regardless of the cumulative dose and were excluded from further analysis. Patients in the high-OCS and no-OCS groups were matched in a 1:1 ratio by age (in years), sex, and region. Because COPD has a known association with comorbidities, such as osteoporosis and infections[10,11] that might also be attributed independently to OCS use, we stratified our results by the presence of COPD.

Study Variables

The main outcome of interest was the risk of possible corticosteroid-related AE, which was identified by using medical claims from 2008 to 2009. We focused on bone-related conditions, pneumonia, opportunistic infections, hypertension, diabetes mellitus, glaucoma, cataracts, lipid disorders, obesity, and peptic ulcer disease, and these conditions were all identified by using International Classification of Diseases, Ninth Revision, Clinical Modification codes (Supplemental Appendix Table 1). The primary predictor variable was exposure to OCS, which we measured as the prednisone-equivalent dose in milligrams based on all medication fills in the study period. Additional variables included patient demographics as well as treatment- and disease-related characteristics. Usual physician specialty was defined as the specialty with the largest number of office visits with evaluation and management services during the study period.[1] An analogous measure was constructed for "usual asthma physician specialty" based on evaluation and management visits with an asthma diagnosis only. As a proxy for the general level of illness, we reported the number of chronic conditions calculated by using a previously validated method.[12] Asthma-related resource utilization was defined as any asthma-related (primary diagnosis of asthma) hospitalization or emergency department visit and the number of short-acting β-agonist prescriptions filled. Other variables included ICS and ophthalmic corticosteroid use.

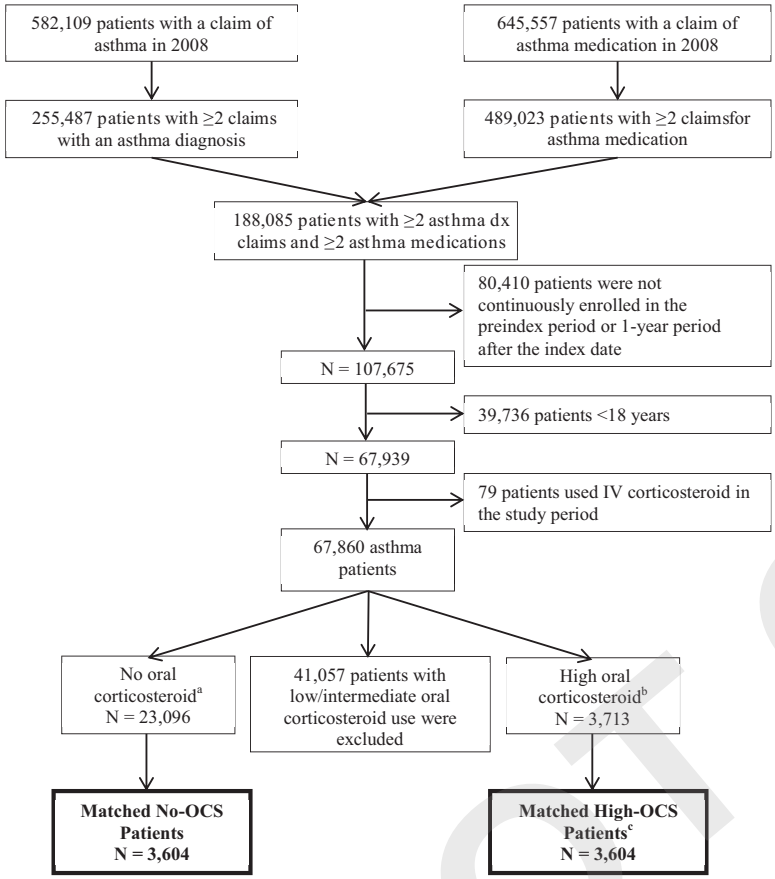
Table 1 **Proportions of patients with asthma associated with specific levels of OCS exposure in 1 year***

Cumulative Prednisone-Equivalent Exposure, mg	Cumulative Percentage of Patients	
	Patients With <30 Total Days of Supply (N = 29,272)#	Patients With ≥30 Total Days of Supply (N = 7851)§
50	0.50	0.03
250	50.39	1.78
500	82.16	8.99
750	94.45	21.70
1000	98.55	36.50
1250	99.53	49.74
1500	99.83	59.84
1750	99.91	66.20
2000	99.94	73.11
2250	99.95	77.25
2500	99.97	80.93
>2500	100	100

**Adapted from Ref. 9.*
#Median cumulative OCS dose was 250 mg.
§Median cumulative OCS dose was 1260 mg.

Statistical Analysis

Descriptive statistics, including means (standard deviations), medians, and percentages, were reported for all measures, stratified by high OCS versus no OCS as applicable. We used χ^2 tests and t-tests to compare categorical and continuous variables, respectively. We compared



[a] No fills of oral corticosteroids in 2008 and 2009.
[b] Patients who filled at least 30 days of supply of oral corticosteroids in both 2008 and 2009.
[c] There were 109 high-OCS patients who could not be matched to no-OCS patients; these patients were excluded.

Figure 1. *Identification flowchart for patients with claims of asthma.*

the prevalence of possible corticosteroid AEs between the high-OCS and no-OCS cohorts, with and without further stratification by COPD diagnosis. A logistic regression model was used to determine if remaining differences between groups on ICS exposure explained between-group differences in AE frequency. All data transformations and statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC). All tests were two-sided, with a significance level of 0.05.

RESULTS

Patient Characteristics

We identified 188,085 patients with asthma, excluding 80,410 who were not continuously enrolled, 39,736 who were <18 years old, and 79 who used IV corticosteroids. We identified matches for 3604 of 3713 patients (97%) who met the definition of high OCS use. The final study group comprised these 3604 patients in the high-OCS group and their 3604 patients as the no-OCS matched controls (Fig. 1). The mean age of the matched cohorts was 54.4 years, and 68.1% were female (Table 2). Approximately 44.9% had a diagnosis of COPD. Unmatched patient and provider-level characteristics are provided in Table 3.

Matched Clinical Characteristics and Resource Utilization

After matching, age, sex, region, and COPD status were identical between the groups. Patients in the high-OCS groups had statistically significantly more chronic conditions than their counterparts in the no-OCS group (6.4 versus 5.4). The physician specialty that provided overall care and asthma-related care was statistically significantly different between that high- and no-OCS groups ($p < 0.001$), with patients in the high-OCS group less likely to have a primary care physician provide their usual care (53.9% versus 65.2%) and less likely to provide their usual asthma care (44.0% versus 51.9%). Patients in the high-OCS group had a mean prednisone-equivalent dose exposure of 4592 mg during the study period, compared with 0 mg for the no-OCS group. They also tended to

Table 2 **Patient demographics, before and after cohort matching**

Patient Characteristic	Before Match		After Match	
	No OCS (N = 23,096)	High OCS (N = 3713)	No OCS (N = 3604)	High OCS (N = 3604)*
Age, mean ± SD, y	47.6 ± 14.7	54.3 ± 12.7	54.4 ± 12.7	54.4 ± 12.7
Age category, no. (%)				
18–34 y	4725 (20.5)	254 (6.8)	239 (6.6)	239 (6.6)
35–44 y	4728 (20.5)	522 (14.1)	505 (14.0)	505 (14.0)
45–54 y	5803 (25.1)	1042 (28.1)	1017 (28.2)	1017 (28.2)
55–64 y	5281 (22.9)	1225 (33.0)	1197 (33.2)	1197 (33.2)
≥65 y	2559 (11.1)	670 (18.0)	646 (17.9)	646 (17.9)
Female, no. (%)	14,484 (62.7)	2530 (68.1)	2453 (68.1)	2453 (68.1)
Geographic region, no. (%)				
Midwest	5560 (24.1)	982 (26.4)	932 (25.9)	932 (25.9)
Northeast	3481 (15.1)	460 (12.4)	438 (12.2)	438 (12.2)
South	9470 (41.0)	1697 45.7)	1684 (46.7)	1684 (46.7)
West	4585 (19.9)	574 (15.5)	550 (15.3)	550 (15.3)
Diagnosis of COPD	3242 (14.0)	1726 (46.5)	1618 (44.9)	1618 (44.9)

SD = Standard deviation.
**A total of 109 patients who used high doses of OCS were excluded because no nonuse matches were found in the data set.*

Table 3 **Unmatched patient and provider characteristics in the matched study cohorts (total N = 7208)**

Patient or Provider Characteristic	No OCS	High OCS	p Value
Provider characteristics			
Usual physician specialty, no. (%)			<0.001
Primary care	2351 (65.2)	1941 (53.9)	
Allergist	342 (9.5)	323 (9.0)	
Pulmonologist	242 (6.7)	555 (15.4)	
Other/unknown	669 (18.6)	785 (21.8)	
Usual asthma physician specialty, no. (%)			<0.001
Primary care	1869 (51.9)	1585 (44.0)	
Allergist	699 (19.4)	602 (16.7)	
Pulmonologist	600 (16.6)	1009 (28.0)	
Other/unknown	436 (12.1)	408 (11.3)	
Medication use			
OCS dose, mean (SD)*	—	4591.9 ± 3605.3	—
No. ICS canisters filled, mean ± SD	7.0 ± 7.79	9.2 ± 9.66	<0.001
No. ICS canisters filled, no. (%)			
0	822 (22.8)	735 (20.4)	<0.001
1–6	1299 (36.0)	1109 (30.8)	
7–12	689 (19.1)	656 (18.2)	
≥13	794 (22.0)	1104 (30.6)	
No. short-acting β-agonist prescriptions filled, mean ± SD	3.8 ± 5.4	8.1 ± 9.71	<0.001
Ophthalmic steroid prescriptions filled, no. (%)	251 (7.0)	364 (10.1)	<0.001

SD = Standard deviation.
**Prednisone-equivalent dose in milligram.*

fill more ICS and short-acting β-agonist prescriptions, used more ophthalmic steroids, and visited the emergency department more frequently, and they were hospitalized more often for asthma-related issues than patients in the no-OCS group.

Incremental Risk of AEs in High-OCS Users

Patients in the high-OCS group had a higher overall rate of possible corticosteroid-related AEs than patients in the no-OCSgroup (83.5% versus 78.1%, $p <$ 0.001) (Table 4), an incremental risk of 5.4%. Hyperten-

Table 4 **Potential corticosteroid AEs in matched cohorts, with and without the presence of COPD (N = 7208)**

AE	All Matched Patients (N = 7208)			Patients Stratified by COPD (N = 7208)					
				Patients Without COPD (n = 3972)			Patients With COPD (n = 3236)		
	No OCS, no. (%)	High OCS, no. (%)	p Value	No OCS, no. (%)	High OCS, no. (%)	p Value	No OCS, no. (%)	High OCS, no. (%)	p Value
Any AE	2816 (78.1)	3011 (83.5)	<0.001	1380 (69.5)	1508 (75.9)	<0.001	1436 (88.8)	1503 (92.9)	<0.001
Bone-related conditions	210 (5.8)	359 (10.0)	<0.001	72 (3.6)	135 (6.8)	<0.001	138 (8.5)	224 (13.8)	<0.001
Osteoporosis	155 (4.3)	274 (7.6)	<0.001	55 (2.8)	99 (5.0)	<0.001	100 (6.2)	175 (10.8)	<0.001
Fractures	72 (2.0)	107 (3.0)	0.008	19 (1.0)	44 (2.2)	0.001	53 (3.3)	63 (3.9)	0.344
Pneumonia	394 (10.9)	1022 (28.4)	<0.001	98 (4.9)	340 (17.1)	<0.001	296 (18.3)	682 (42.2)	<0.001
Opportunistic infections	13 (0.4)	54 (1.5)	<0.001	5 (0.3)	27 (1.4)	<0.001	8 (0.5)	27 (1.7)	0.001
Hypertension	2049 (56.9)	2268 (62.9)	<0.001	900 (45.3)	1029 (51.8)	<0.001	1149 (71.0)	1239 (76.6)	<0.001
Diabetes mellitus	1024 (28.4)	1227 (34.0)	<0.001	420 (21.1)	513 (25.8)	<0.001	604 (37.3)	714 (44.1)	<0.001
Glaucoma	134 (3.7)	166 (4.6)	0.059	66 (3.3)	67 (3.4)	0.930	68 (4.2)	99 (6.1)	0.014
Cataracts	192 (5.3)	244 (6.8)	0.010	68 (3.4)	85 (4.3)	0.161	124 (7.7)	159 (9.8)	0.029
Lipid disorders*	2187 (60.7)	1988 (55.2)	<0.001	1056 (53.2)	975 (49.1)	0.010	1131 (69.9)	1013 (62.6)	<0.001
Obesity	617 (17.1)	700 (19.4)	0.011	280 (14.1)	326 (16.4)	0.042	337 (20.8)	374 (23.1)	0.116
Peptic ulcer disease	7 (0.2)	8 (0.2)	0.796	1 (0.1)	3 (0.2)	0.317	6 (0.4)	5 (0.3)	0.763

**Percentages of patients who filled any antihyperlipidemic medication in either 2008 or 2009 among nonusers and high-OCS users were 41.5% and 38.3% for the overall cohort, 34.5% and 30.8% for the no-COPD cohort, and 51.1% and 48.6% for the COPD cohort.*

sion (62.9%), lipid disorders (55.2%), and diabetes (34.0%) were the three most common potential corticosteroid AEs identified in the high-OCS cohort. Individually, most potential AEs were seen in significantly higher proportions among patients versus the high-OCS group, including hypertension (62.9% in the high-OCS versus 56.9% in the no-OCS group), diabetes (34.0% versus 28.4%), pneumonia (28.4% versus 10.9%), obesity (19.4% versus 17.1%), osteoporosis (7.6% versus 4.3%), cataracts (6.8% versus 5.3%), and opportunistic infections (1.5% versus 0.4%) (cataracts, $p = 0.01$; obesity, $p = 0.011$; all others, $p < 0.001$). There were no significant differences in the rates of glaucoma and peptic ulcer disease, whereas lipid disorders were significantly less prevalent in patients in the high-OCS group than in patients in the no-OCS group (55.2% versus 60.7%; $p < 0.001$). The highest incremental risk among AEs was for pneumonia (17.5% higher in patients in the high-OCS group).

Incremental Risk of AEs in Patients in the High-OCS Group by COPD Status

Patients were stratified by the presence or absence of COPD (Table 4). The incremental risk of any potential AE in patients in the high-OCS group was 6.4% higher among patients without COPD (75.9% in patients in the high-OCS group versus 69.5% in the no-OCS group, $p < 0.001$). The risk was increased by 4.1% in those with COPD (92.9% versus 88.8%, $p < 0.001$). The pattern of increased risk in both patients with COPD and those without COPD was nearly identical to the overall comparison between all patients in the high-OCS and no-OCS groups. Risks of potential AEs were significantly higher in patients in the high-OCS group compared with nonusers for pneumonia (increased by 12.2% in patients without COPD and by 23.9% in patients with COPD), bone-related conditions (without COPD increased 3.2%, with COPD increased 5.3%), and opportunistic infections (without COPD increased 1.1%, with COPD increased 1.2%) Hypertension, diabetes, and obesity were all statistically significantly more prevalent among users of high doses OCS in both the COPD and non-COPD groups. Lipid disorders were significantly less prevalent among users of high doses OCS users than nonusers in both COPD and non-COPD groups.

DISCUSSION

The risk of a broad range of potential AEs known to be associated with OCS use is statistically significantly higher in patients with asthma who fill 30 days or more of OCS per year for 2 years than in patients who did

not use OCS. The risk of any of the studied potential AEs is statistically significantly elevated in both patients with COPD and those without COPD who used high amounts of OCS. The magnitude of risk in both patients with COPD and those without COPD (an increase of 4.1% in COPD and 6.4% in non-COPD) is similar to what has been seen in other studies.[3,4] The results are biologically plausible given what is known about the impact of corticosteroids on immunity, bone formation, endocrine function, and other body systems. As a result of their known risks, OCS are recommended only for acute exacerbations and for patients who have inadequate response to inhaled ICS and inhaled long-acting β-agonists and other long-term controllers. However, we found OCS use to be common: 60% of patients with asthma filled at least one OCS prescription over a 2-year period, and 5.4% filled at least a 30 days of supply each year for two consecutive years. Corticosteroids inhibit T-cell activation and suppress proinflammatory cytokine production, which leads to significant immunosuppressive effects.[4] Not surprisingly, the risk of infectious conditions showed the largest increase with OCS use. The risk of pneumonia in patients who use high doses of OCS is 2.3- to 3.5-fold that of the patients who do not use OCS, and the risk of opportunistic infections is 3.4- to 4.7-fold that of nonusers. Although we could not directly establish the severity of these opportunistic infections, we limited our analysis to those conditions recognized as most serious (*e.g.*, severe or disseminated candidiasis, disseminated herpes zoster, severe herpes simplex) (Supplemental Appendix Table 1).

An unexpected finding was the higher rate of lipid disorders in patients in the non-OCS group compared with the high-OCS group. We considered four possible explanations for this finding. First, there might be an unmeasured covariate that is unequally distributed between the groups. For example, some risk factor for lipid disorders might be more common in the non-OCS group of users (*e.g.*, obesity, family history of hyperlipidemia). Statins have been demonstrated in large cohort studies to be prescribed more often in patients with higher cardiovascular risk.[13,14] If the cardiovascular risk factor did not appear in claims, we would be unable to identify or adjust for it. Second, this could be a chance finding and not reflective of an actual underlying difference between the groups (the identification of a statistically significant difference at the $p < 0.05$ level means the probability is 5% that the finding occurred by chance). Third, there may be a direct, causal relationship between the use of OCS and lower lipids (*e.g.*, OCS use reduces lipid levels). However, we found no literature to support this proposition, and, indeed, some evidence refutes it. Fourth, the direction of causality could be reversed, and physicians may be reluctant to prescribe OCS to patients with elevated lipids, perhaps because of concern over the potential adverse cardiovascular effects of OCS on a population already at risk. A study designed to test this hypothesis would require a different design than the one we undertook and could be considered in the future.

Although OCS use is known to carry risk, there has been relatively little research that estimates the magnitude of the risk specifically in patients with asthma. Zazzali *et al.*[15] demonstrated that, among adult patients with asthma, every 1000 mg increase in OCS was associated with a 3% higher risk of osteoporosis, 2% higher risk of fracture, and 2% higher risk of cataracts. The overall prevalence of AEs in this population is consistent with previous research that used different study designs.[6,7] Our results appear to be consistent with previous epidemiologic studies that examined comorbidities and resource utilization in similar populations.[16,17]

A key strength of our study was that we were able to implement a practical, clinically relevant definition of high OCS use ($\geq$30 days of supply) to measure the outcomes of patients with asthma. This threshold was established in an exploratory analysis of more than 37,000 patients with asthma.[9] A systematic review of the cumulative medical and economic burden of OCS use concluded that a dose-response relationship exists between higher OCS doses and the risk of various AEs but that variation based on specific OCS therapies has not been well characterized.[2] Potential areas for future research include further confirmation of what is confirmation of "high" or "low" OCS dose thresholds, the definitions of which remain controversial.[5,6,18,19] Validation of our findings with multiple levels of OCS use and/or other patient populations (including Medicaid patients and other commercially insured patients) would be valuable.

The study had limitations. Observational studies cannot establish causation, and we have no direct evidence that observed OCS prescription fills resulted in the observed increase in AEs. Distinguishing between an underlying (preexisting) comorbidity and a true AE that results from OCS use may be difficult in any setting,[18] and is particularly difficult when using administrative claims. We used a matched and stratified study design to control for potential confounding. The resulting difference in prevalence should represent the effect of the independent variable. The prevalence of potential AEs in patients who are high OCS users was 83.5% overall (75.9% without COPD, 92.9% with COPD), consistent with previously published reports by Curtis *et al.*[6] (90%) and Fardet *et al.*[7] (up to 63.0%). Matching is only possible on variables available in the data base, and claims do not contain many variables, which may have confounded our analysis. Smoking, which increases the risk of a certain number of the observed AEs, is not coded reliably, and race and body mass index are not coded at all. So, for

example, if smokers with COPD were more likely to be prescribed OCS, then our results could be biased. Studies that use clinical data would be useful to confirm our findings. We did attempt to control for asthma severity because users of OCS and nonusers would be expected to differ substantially in severity. However, the matched groups differed significantly in the number of ICS canisters used. To control for potential confounding by ICS use, we conducted a regression model after matching to control for ICS (data not shown). The model confirmed both that ICS did not predict AEs and that there was statistically significant increase in the odds of AE in the users of high amounts of OCS, even after controlling for ICS.

Other limitations of this study were those inherent in claims data bases, including coding errors and a lack of clinical detail. Health care claims data bases are retrospective and collected for billing and not for research purposes. Claims data generally lack information on dosing of IV medications, such as detail on IV corticosteroid dose. We, consequently, excluded 79 patients who used IV steroids, although these patients comprised too small a sample to have meaningfully affected the results. Finally, the data base does not contain uninsured patients, who may have different demographics, comorbidities, and medication utilization patterns.[19]

In conclusion, patients with asthma who filled OCS prescriptions that covered 30 days a year for 2 years had a significantly greater prevalence of potential corticosteroid-related AEs, such as pneumonia and bone-related conditions, than age, sex, and COPD-status matched patients who filled no OCS prescriptions. The incremental risk of AEs overall is 5.4% in patients with high OCS use. Rates of potential AEs are statistically significantly higher both in patients with asthma and with COPD and in those patients without COPD. Long-term OCS use adversely affects multiple organ systems. Reducing corticosteroid use by better adherence to expert guidelines[1] and by developing corticosteroid-sparing treatments with comparable or improved efficacy and effectiveness are both critical steps to minimize the AEs of therapy. Research that builds on our definition of high OCS use may provide the groundwork for more specific policy recommendations regarding measures to prevent or screen for potential AEs in patients with asthma who use high doses of OCS.

REFERENCES

1. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda: National Heart, Lung, and Blood Institute (US); 2007 Aug. Available online at http://www.ncbi.nlm.nih.gov/books/NBK7232/; accessed May 14, 2014.
2. Manson SC, Brown RE, Cerulli A, and Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med 103:975–994, 2009.
3. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 9:30, 2013.
4. van Staa TP, Leufkens HGM, and Cooper C. The epidemiology of corticosteroid-induced osteoporosis: A meta-analysis. Osteoporos Int 13:777–787, 2002.
5. Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: Published evidence and prospective trial data. Ann Rheum Dis 65:285–293, 2006.
6. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 55:420–426, 2006.
7. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: Frequency, risk factors and patient's opinion. Br J Dermatol 157:142–148, 2007.
8. Schatz M, Broder M, Chang E, et al. Asthma quality-of-care measures using administrative data: Identifying the optimal denominator. Ann Allergy Asthma Immunol 102:98–102, 2009.
9. Zazzali JL, Raimundo K, Chang E, et al. Defining high oral corticosteroid use in asthma patients. American Thoracic Society International Meeting. San Diego, California, May 18, 2014.
10. Mullerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: A population database analysis. Respir Med 106:1124–1133, 2012.
11. Vanfleteren LE, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 187:728–735, 2013.
12. Chronic Condition Indicator (CCI) for ICD-9-CM. Summary and downloading information. Oct 2009. Agency for Health Care Policy and Research, Rockville, MD. Available online at http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp; accessed May 14, 2014.
13. Berthold HK, Gouni-Berthold I, Böhm M, et al. Patterns and predictors of statin prescription in patients with type 2 diabetes. Cardiovasc Diabetol 8:25, 2009.
14. Gulliford MC, Charlton J, and Latinovic R. Trends in antihypertensive and lipid-lowering therapy in subjects with type II diabetes: Clinical effectiveness or clinical discretion? J Hum Hypertens 19:111–117, 2005.
15. Zazzali JL, Broder M, and Chang E. Oral corticosteroid use increases the risk of glucocorticoid-related adverse events in asthmatics. American Academy of Allergy, Asthma, & Immunology Annual Meeting. San Diego, California, March 4, 2012.
16. Aubas C, Bourdin A, Aubas P, et al. Role of comorbid conditions in asthma hospitalizations in the south of France. Allergy 68:637–643, 2013.
17. Diette GB, Krishnan JA, Dominici F, et al. Asthma in older patients: Factors associated with hospitalization. Arch Intern Med 162:1123–1132, 2002.
18. McDonough AK, Curtis JR, and Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol 20:131–137, 2008.
19. Wilper AP, Woolhandler S, Lasser KE, et al. A national study of chronic disease prevalence and access to care in uninsured U.S. adults. Ann Intern Med 149:170–176, 2008. □