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Risk of Corticosteroid-Related Adverse Events in Patients With Asthma With 30 Days or More of Annual Oral Corticosteroid Exposure

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INTRODUCTION

- Corticosteroids, whether chronic or intermittent, are a treatment option for patients with severe asthma.
- While their use is generally thought to increase the risk of a variety of adverse events, little is known about the quantitative impact of corticosteroid usage in asthma specifically.[1]
- Potential glucocorticoid-related adverse events (GAEs) encompass a variety of other conditions, including osteoporosis, serious infections, diabetes and impaired glucose tolerance, hypertension, obesity, and other cardiovascular risk factors.[2]

OBJECTIVE

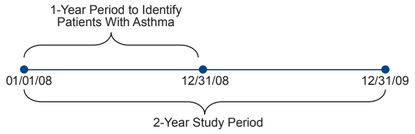
- This study aims to determine the incremental risk of GAEs of high-dose exposure compared with no dose exposure to oral corticosteroids (OCS) in patients with asthma.

METHODS

Study Design

- Retrospective matched cohort study, using a commercial health care claims database in the period of 2008 and 2009 (**Figure 1**).

Figure 1. Study Design



Inclusion Criteria

- ≥2 medical claims with asthma as 1 of the listed diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification code of 493.x) in 2008; and
- ≥2 asthma medication fills in 2008; and
- Aged ≥18 years at the end of 2008.

Exclusion Criteria

- Not continuously enrolled during the 2-year study period; or
- Any intravenous corticosteroid medication use (because the dose of these medications cannot be determined).

Definition of Study Cohorts

- High OCS cohort: high OCS use was defined as ≥30 days of combined use each year for both 2008 and 2009, regardless of dose.
- No OCS cohort: no OCS use was defined as those with no fill of OCS in both 2008 and 2009.

Matched Cohort

- Patients were stratified by chronic obstructive pulmonary disease (COPD) status and then, using an exact match on age, sex, and region, each high OCS user was matched 1:1 with a non-OCS user. Patients without a match were excluded from the final cohort.

Definition of GAEs

- GAEs were defined based on the current literature and expert opinion as hypertension, diabetes, lipid disorder, glaucoma, opportunistic infection, pneumonia, obesity, cataract, peptic ulcer disease, and bone-related conditions.

Statistical Analysis

- All variables used to identify the matched cohort were compared between OCS use groups both before matching (all patients) and after matching (final study cohort).
- For the final matched study cohorts, all measures were reported, stratified by the high OCS use versus the no OCS use groups.
- The GAE rate in the no OCS use group was used as the baseline rate, and the difference between the baseline rate and GAE rate in the high OCS use group was reported as incremental risk.
- To control for confounding factors, all analyses were repeated for patients with and without COPD.
- Descriptive statistics, including means, standard deviations, medians, and percentages, were reported for all measures whenever applicable.
- Chi-square tests were used to compare the prevalence of these GAEs among patients with high OCS use versus no OCS use.
- All data transformations and statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC).
- All tests were 2-sided with a significance level of 0.05.

RESULTS

- Among all 67,860 patients with asthma identified, 23,096 patients did not use OCS and 3,713 were high OCS users.
  - Mean age was 47.8 years, 67.2% of patients were female, and the majority (46.0%) lived in the southern region of the United States.
- From the original cohort of patients with asthma, 3,604 non-OCS users were exactly matched with 3,604 high OCS users based on age, sex, region, and COPD status (**Table**).
- Patients were not matched by physician characteristics or chronic conditions/comorbidities.
- 109 (2.9%) patients were not able to be matched and were excluded from the final cohort.

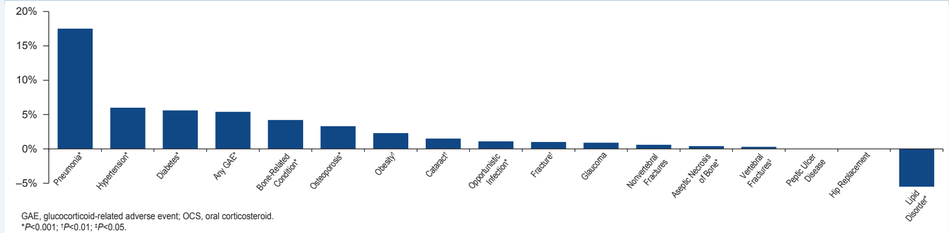
Table. Patient Demographics*

	Matched† No Use,‡ n=3,604	Matched† High Use,§ n=3,604	Unmatched High Use,§ n=109
Age, y, mean (SD)	54.4 (12.7)	54.4 (12.7)	51.8 (14.4)
18–34, n (%)	239 (6.6)	239 (6.6)	15 (13.8)
35–44, n (%)	505 (14.0)	505 (14.0)	17 (15.6)
45–54, n (%)	1,017 (28.2)	1,017 (28.2)	25 (22.9)
55–64, n (%)	1,197 (33.2)	1,197 (33.2)	28 (25.7)
≥65, n (%)	646 (17.9)	646 (17.9)	24 (22.0)
Female, n (%)	2,453 (68.1)	2,453 (68.1)	77 (70.6)
Region, n (%)			
Midwest	932 (25.9)	932 (25.9)	50 (45.9)
Northeast	438 (12.2)	438 (12.2)	22 (20.2)
South	1,684 (46.7)	1,684 (46.7)	13 (11.9)
West	550 (15.3)	550 (15.3)	24 (22.0)
COPD	1,618 (44.9)	1,618 (44.9)	108 (99.1)

COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroid; SD, standard deviation.
*No statistically significant (at $P<0.05$) differences between matched groups for any of the matched variables.
†Exactly matched in age (in y), sex, region, and COPD.
‡No use of OCS in 2008 and 2009.
§Patients who had ≥30 days of supply in both 2008 and 2009.

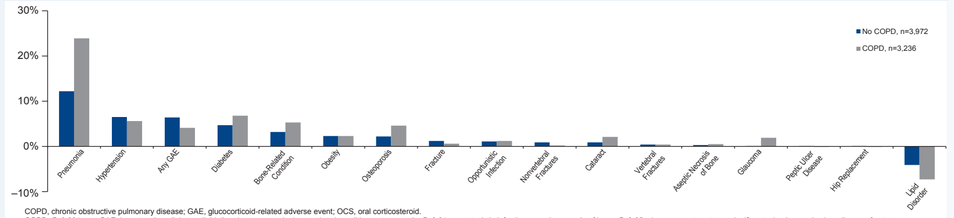
- Within the matched cohorts, high OCS users had a significantly higher rate of GAEs compared with non-OCS users (**Figure 2**).
  - Any GAEs: 83.5% versus 78.1%; incremental risk: 5.4%; $P<0.001$.
  - Pneumonia: 28.4% versus 10.9%; incremental risk: 17.5%; $P<0.001$.
  - Bone-related conditions: 10.0% versus 5.8%; incremental risk: 4.2%; $P<0.001$.
  - Opportunistic infections: 1.5% versus 0.4%; incremental risk: 1.1%; $P<0.001$.
- Lipid disorders were less prevalent in high OCS users compared with non-OCS users (55.2% vs 60.7%; $P<0.001$).
- When stratifying by COPD, high OCS users had higher GAE rates in terms of overall adverse events and bone-related complications, opportunistic infections, and pneumonia in both the COPD and non-COPD groups (**Figure 3**).
  - Patients with COPD overall had higher rates of GAEs (high OCS use: 92.9%; no OCS use: 88.8%) compared with patients without COPD (high OCS use: 76.0%; no OCS use: 70.0%).
  - The incremental risk of pneumonia in patients with COPD with high OCS use was higher than in patients without COPD (23.9% vs 12.2%).
  - Rates of lipid disorder were higher in patients with COPD (high OCS use: 62.6%; no OCS use: 69.9%) than in patients without COPD (high OCS use: 49.0%; no OCS use: 53%).
- Lipid disorders were less prevalent in high OCS users than in non-OCS users, regardless of COPD status.

Figure 2. Incremental Risk of GAE Associated With High OCS Exposure (Matched Cohort)



GAE, glucocorticoid-related adverse event; OCS, oral corticosteroid.
*$P<0.001$; †$P<0.01$; ‡$P<0.05$.

Figure 3. Incremental Risk of GAE Associated With High OCS Exposure (Matched Cohort, Stratified by COPD Status)



COPD, chronic obstructive pulmonary disease; GAE, glucocorticoid-related adverse event; OCS, oral corticosteroid.
COPD: $P<0.001$: any GAE, hypertension, diabetes, lipid disorder, pneumonia, bone-related condition, osteoporosis; $P<0.01$: opportunistic infection, aseptic necrosis of bone; $P<0.05$: glaucoma, cataract; nonsignificant: obesity, peptic ulcer disease, fracture, nonvertebral fractures, vertebral fractures, hip replacement. No COPD: $P<0.001$: any GAE, hypertension, diabetes, opportunistic infection, pneumonia, bone-related condition, osteoporosis; $P<0.01$: fracture, nonvertebral fractures; $P<0.05$: lipid disorder, obesity, aseptic necrosis of bone; nonsignificant: glaucoma, cataract, peptic ulcer disease, hip replacement.

LIMITATIONS

- Limitations of this study are the ones inherent in claims databases.
- A few conditions, such as peptic ulcer disease, were too uncommon to derive meaningful conclusions.
- Other GAEs, particularly hypertension and diabetes mellitus, are common comorbidities in US adults. Distinguishing between a preexisting comorbidity and a true GAE resulting from OCS use may be difficult, and in some cases GAE rates may be overestimated (eg, lipid disorders).
- Finally, the database does not contain uninsured patients, who may have different demographics, comorbidities, and medication utilization patterns.

CONCLUSIONS

- Patients with asthma, particularly those treated with OCS for ≥30 days annually regardless of dose, have a very high prevalence of GAEs, such as pneumonia, opportunistic infections, and bone-related conditions.
- The incremental risk of GAEs overall is 5.4% with high-dose OCS use. The rates of GAEs are even higher in patients with asthma who also have COPD compared with those without COPD.
- Although there is no standardized definition of a clinically meaningful incremental risk for these GAEs, the increased risks that we have quantified appear to be nontrivial.

REFERENCES

1. van Staa TP, et al. *Osteoporos Int.* 2002;13:777–87. 2. McDonough AK, et al. *Curr Opin Rheumatol.* 2008;20:131–7.

DISCLOSURES

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