Rationale: Oral corticosteroids (OCSs) are a mainstay of asthma therapy for managing severe symptoms and exacerbations. Prolonged systemic exposure to glucocorticoids is known to be associated with increased risk of glucocorticoid-related adverse events (GAEs). Our objective was to determine the risk of GAEs associated with cumulative OCS exposure in asthmatics.

Methods: Retrospective cohort analysis of adult asthmatics using a HIPAA-compliant claims database. Patients were continuously enrolled during 2002-2003 and were followed until the end of enrollment or study end (2007), whichever was earlier (median= 1,461 days observation). Patients with potential GAEs in the first year were excluded. Cox regression models estimated adjusted hazard ratios (HRs) of the risk of GAEs (osteoporosis, fracture, and cataracts) for different OCS exposure levels, measured by cumulative prednisone-equivalent dose as recorded on pharmacy claims, while adjusting for age, gender, region, usual-care physician specialty, and chronic conditions.

Results: We examined 37,891 asthmatics (mean age = 44.9 years, 65.7% female). For every 1,000-mg increase in prednisone-equivalent OCS exposure, the risk of a claim for osteoporosis was 3% higher (HR = 1.03, $P < 0.001$), the risk of a claim for fracture was 2% higher (HR = 1.02, $P < 0.001$), and the risk of a claim for cataracts was 2% higher (HR = 1.02, $P < 0.001$).

Conclusions: In asthmatics, greater cumulative OCS exposure is associated with statistically significant increased risks of osteoporosis, fracture, and cataracts.

#278 Oral Corticosteroid Use Increases the Risk of Glucocorticoid-Related Adverse Events in Asthmatics

James L. Zazzali, PhD, MPH[1]; Michael S. Broder, MD, MSHS[2]; Eunice Chang, PhD[2]

[1] Genentech, 1 DNA Way, South San Francisco, CA 94080;[2] Partnership for Health Analytic Research, 280 S. Beverly Dr., Suite 404, Beverly Hills, CA 90212

Introduction

- Oral corticosteroids (OCSs) are a mainstay of asthma treatment, recommended in the National Heart, Lung, and Blood Institute's Expert Panel Report 3 both as long-term treatment for severe persistent asthma and in short bursts as an adjunct to short-acting beta-agonists (SABAs) for moderate and severe exacerbations.[1]
- OCSs are linked to a variety of side effects, termed glucocorticoid-related adverse events (GAEs). An increased risk of GAEs has been linked to greater dose, frequency, and duration of OCS use.[2]
- The magnitude of the risk associated with GAEs has not been previously well characterized in asthma, particularly that associated with multiple bursts.

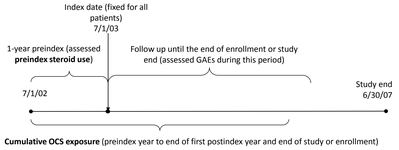
Objective

- To determine the extent to which the use of oral steroids in patients with asthma increases the risk of GAEs.

Methods

- This was a retrospective cohort analysis using a HIPAA-compliant administrative claims database with data for 10 million US individuals. The database contains adjudicated pharmacy and medical claims for each physician visit, medical procedure, hospitalization, drug dispensed, and test performed. All major regions of the US are represented in the data.
- The study population included adults with ≥2 asthma diagnosis claims who had filled ≥2 asthma medications in the preindex period.

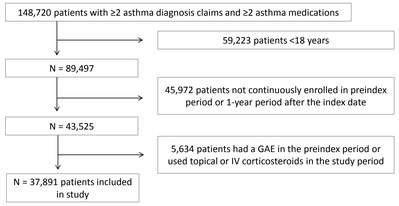
Figure 1. Study Time Frame



- To avoid confounding, patients with potential GAEs of interest during the preindex period and patients with <2 years of continuous enrollment were excluded.
- Preindex oral steroid use groups were defined: **current** use (steroid available to the patient on the day the variable was calculated); **recent** use (last use within 90 days); **distant** use (last use >90 days but <180 days prior); **remote** use (last use >180 days but <365 days prior); **no** use in last 365 days.
- The GAEs of interest in this study were those felt to be caused by steroids AND identifiable as discrete events using ICD-9-CM claims: cataracts, fractures, osteoporosis, upper gastrointestinal complications, aseptic necrosis of bone, and hip replacement.
- Potential GAEs such as acne, sleep problems, and weight gain were excluded because they were unlikely to be recorded in claims.
- Cumulative OCS exposure was converted to a cumulative prednisone-equivalent dose using published data.[3]
- Cox regression models were used to estimate hazard ratios for the risk of GAEs given different OCS exposure levels, adjusting for age, gender, region, physician specialty, comorbidities, and asthma severity (using a variety of measures including asthma care Step).[4] To account for differing levels of OCSs at different time points, OCS exposure was entered in the model as a time-dependent variable (updated daily).

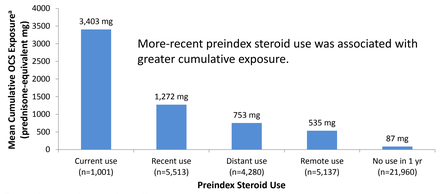
Results

Figure 2. Cohort Selection



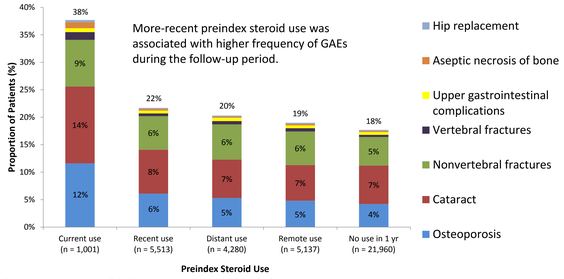
- Patients were observed for a median of 4 years (1,461 days).
- Mean patient age was 44.9 years, and 65.7% were female.
- Primary care providers were the most common source of asthma care (57.3%), compared with allergists (22.9%), pulmonologists (12.5%), and others/unknown (7.3%).
- Patients were classified into Steps of asthma therapy by medications used, with 11.6% in Step 1, 22% Step 2, 23.7% Step 3, 22.2% Step 4, 9% Step 5, 0.4% Step 6, and 11.1% unclassifiable.
- 4.7% of patients had at least 1 asthma-related hospitalization in the preindex year, and 6.3% had at least 1 asthma-related ED visit.

Figure 3. Mean Cumulative OCS Exposure[a] Per Patient by Preindex Steroid Use



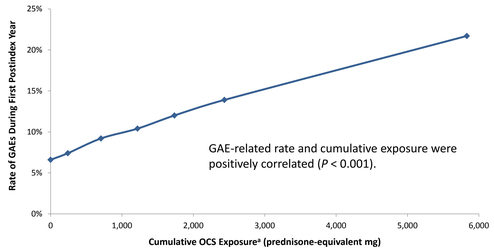
[a]From preindex year to end of first postindex year.

Figure 4. Proportion of Patients Experiencing a GAE During the Follow-Up Period[a] by Preindex Steroid Use



[a]Patients were followed from 7/1/03 (the index date) until 6/30/07 or the end of enrollment, whichever was earlier.

Figure 5. Relationship Between Cumulative OCS Exposure[a] and Rate of GAEs



Cumulative OCS exposure range[a] (mg)	0	1-500	501–1,000	1,001-1,500	1,501-2,000	2,001-3,000	3,001-26,770
No. of patients at each range of exposure	17,177	11,789	4,331	1,742	856	837	1,159
GAE-related rate	6.6%	7.4%	9.2%	10.4%	12.0%	13.9%	21.7%
Mean cumulative OCS exposure[a] (mg)	0	241.9	705.6	1,217.4	1,734.3	2,434.9	5,831.1

[a]From preindex year to end of first postindex year.

Table 1. Cumulative OCS Exposure Models: Adjusted Hazard Ratios (HRs)[a] and 95% Confidence Intervals (CIs)

	HR (95% CI)				
	Risk of First GAE	Risk of Bone-Related GAE[b]	Risk of Osteoporosis	Risk of Fracture[c]	Risk of Cataract
Cumulative OCS exposure, per 1,000-mg prednisone equivalent[d]	1.02 (1.017 - 1.024) †	1.02 (1.02 - 1.03) †	1.03 (1.02 - 1.03) †	1.02 (1.02 - 1.03) †	1.02 (1.01 - 1.03) †
Age group (y) * Gender					
Age 18-34: female vs. male	1.16 (0.96 - 1.39)	1.22 (1.00 - 1.49)	2.29 (1.15 - 4.57) ‡	1.13 (0.91 - 1.40)	1.43 (0.74 - 2.77)
Age 35-44: female vs. male	1.41 (1.22 - 1.63) †	1.55 (1.31 - 1.84) †	2.38 (1.60 - 3.52) †	1.49 (1.24 - 1.80) †	1.15 (0.82 - 1.62)
Age 45-54: female vs. male	1.83 (1.64 - 2.03) †	2.45 (2.13 - 2.81) †	6.49 (4.89 - 8.62) †	1.54 (1.30 - 1.83) †	1.19 (1.01 - 1.40) ‡
Age 55+: female vs. male	1.62 (1.51 - 1.74) †	3.31 (2.94 - 3.72) †	5.20 (4.38 - 6.18) †	2.14 (1.83 - 2.50) †	1.02 (0.93 - 1.11)
Female: age 18-34 vs. 55+	0.15 (0.13 - 0.17) †	0.24 (0.21 - 0.27) †	0.05 (0.03 - 0.07) †	0.58 (0.50 - 0.67) †	0.03 (0.02 - 0.04) †
Female: age 35-44 vs. 55+	0.22 (0.21 - 0.24) †	0.33 (0.30 - 0.37) †	0.13 (0.11 - 0.15) †	0.73 (0.64 - 0.82) †	0.07 (0.06 - 0.09) †
Female: age 45-54 vs. 55+	0.48 (0.45 - 0.51) †	0.62 (0.57 - 0.66) †	0.54 (0.49 - 0.59) †	0.77 (0.69 - 0.86) †	0.29 (0.27 - 0.32) †
Male: age 18-34 vs. 55+	0.21 (0.17 - 0.24) †	0.65 (0.53 - 0.79) †	0.11 (0.06 - 0.21) †	1.09 (0.87 - 1.38)	0.02 (0.01 - 0.04) †
Male: age 35-44 vs. 55+	0.26 (0.22 - 0.30) †	0.71 (0.59 - 0.85) †	0.28 (0.19 - 0.41) †	1.04 (0.84 - 1.30)	0.06 (0.05 - 0.09) †
Male: age 45-54 vs. 55+	0.42 (0.38 - 0.47) †	0.83 (0.70 - 0.98) ‡	0.43 (0.31 - 0.59) †	1.07 (0.87 - 1.32)	0.25 (0.21 - 0.29) †
Usual-care physician specialty					
Allergist vs. other	0.86 (0.78 - 0.94)‡	0.92 (0.82 - 1.03)	1.15 (0.98 - 1.36)	0.77 (0.67 - 0.90) †	0.82 (0.71 - 0.95) ‡
Pulmonologist vs. other	0.99 (0.89 - 1.09)	1.03 (0.91 - 1.17)	1.28 (1.08 - 1.51) ‡	0.79 (0.67 - 0.94)	1.00 (0.87 - 1.15)
Primary care vs. other	0.87 (0.81 - 0.93) †	0.89 (0.82 - 0.97) ‡	0.98 (0.87 - 1.11)	0.82 (0.74 - 0.91)	0.88 (0.79 - 0.97) ‡
No. of chronic conditions	1.13 (1.12 - 1.15) †	1.12 (1.10 - 1.13) †	1.08 (1.06 - 1.11) †	1.13 (1.11 - 1.15) †	1.13 (1.11 - 1.15) †
COPD (yes vs. no)	1.23 (1.16 - 1.30) †	1.31 (1.22 - 1.41) †	1.32 (1.20 - 1.45) †	1.36 (1.23 - 1.50) †	1.14 (1.05 - 1.23) ‡
Experienced other GAE (yes vs. no)[d]	N/A	1.22 (1.10 - 1.35) †	1.68 (1.51 - 1.86) †	1.33 (1.18 - 1.50) †	1.25 (1.12 - 1.39) †

[a]Adjusted for age, gender, region, physician specialty, chronic conditions, and presence of COPD.
[b]Osteoporosis, nonvertebral or vertebral fracture, and aseptic necrosis of bone.
[c]Nonvertebral or vertebral fracture.
[d]Time-dependent variable, updated daily.
† P value <0.001.
‡ P value ≥0.001 but <0.05.

- The model estimated that for every 1,000-mg increase in prednisone-equivalent OCS exposure, the risk of a bone-related GAE was 2% higher, the risk of osteoporosis was 3% higher, the risk of fracture was 2% higher, and the risk of cataract was 2% higher.

Conclusions

- In this large cohort of insured asthma patients, 42% had used OCSs during the preindex year. The more recently patients had used steroids, the greater their cumulative OCS exposure (exposure was correlated between baseline and follow-up years).
- Both more-recent preindex steroid use and greater cumulative OCS exposure were associated with GAEs; more-recent users had more such events, and those with more exposure had a higher rate of GAEs.
- The recommended short-course dose of OCSs in adults for acute asthma exacerbation is 280-420 mg; this study suggests that 3-4 courses of OCSs for asthma exacerbations (about 1,000 mg) is enough to increase the risk of osteoporosis by 3%, the risk of cataracts by 2%, and the risk of fracture by 2%.
- Our study is consistent with previously published studies assessing GAE risk[5,6] and is the first to quantify the effect of cumulative OCS exposure on the risk of GAEs in patients with asthma.
- Osteoporosis, cataracts, and nonvertebral fractures were the most common GAEs observed. Patients with a cumulative OCS exposure of 2,001-3,000 mg suffered GAEs at a rate of 13.9% per year. Those with higher exposures had GAEs at a rate of 21.7% per year.
- Women are already at increased risk for developing osteoporosis. Chronic treatment of asthma with OCSs is shown here to further increase this risk.
- Corticosteroids are a mainstay of asthma treatment but are associated with significant long-term consequences, particularly bone-related events. Therapies with steroid-sparing effects should be studied to assess the degree to which they reduce the risk of GAEs in patients with asthma.
- Given the importance of these findings, these results should be confirmed in a prospective study.

Limitations

- This was a retrospective study using health care claims. Claims are collected and processed for payment rather than research purposes and, as a result, may be subject to undercoding or miscoding.
- Claims do not capture data on the severity of GAEs, nor is it possible to identify with certainty the date of onset of each GAE (ie, cataracts may be present for some time before the diagnosis is recorded). We excluded patients with any GAE in the preindex period to minimize the risk of bias.
- Medication information is limited to prescriptions filled. If patients filled but did not use OCSs, this study would have overestimated exposure. No data on the dose of IV or topical steroids were available, and patients using these medications were excluded.

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Please contact James Zazzali, PhD, MPH, for further information: zazzali.james@gene.com

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