Acute and chronic systemic corticosteroid–related complications in patients with severe asthma

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Background: Many patients with severe asthma require maintenance treatment with systemic corticosteroids (SCSs) to control daily symptoms and prevent serious acute exacerbations, but chronic SCS use is associated with complications.

Objective: We sought to evaluate the risk of SCS-related complications by SCS exposure and quantify the associated health care costs and resource use in patients with severe asthma.

Methods: We performed a longitudinal, open-cohort, observational study using health insurance claims data (1997-2013: Medicaid) from Florida, Iowa, Kansas, Missouri, Mississippi, and New Jersey. Eligible patients were 12 years old or older with 2 or more asthma diagnoses and had more than 6 months of continuous SCS use. An open-cohort approach was used to classify patients' follow-up into low, medium, and high SCS exposure (≤ 6, >6-12, and >12 mg/d, respectively). Multivariate generalized estimating equation models were used to estimate the adjusted risk of SCS-related complications for patients with medium and high exposure compared with patients with low exposure and quantify the resulting health care resource use and costs.

Results: The study included 3628 patients (mean age, 57.6 years; 68% female). Patients with medium and high SCS exposure had significantly higher risks of SCS-related complications, including infections and cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications (odds ratio, 1.23-2.12 by complication; $P < .05$ for all but one) versus those with low (reference group) SCS exposure. Medium and high SCS exposure were also associated with significantly more emergency department visits (incidence rate ratios, 1.31 [$P = .0004$] and 1.78 [$P < .0001$]) and inpatient visits (incidence rate ratios, 1.25 [$P < .0001$] and 1.59 [$P < .0001$]) versus low SCS exposure.

Conclusions: A significant dose-response relationship was demonstrated between chronic SCS use and risk of SCS-related complications in patients with severe asthma. Effective SCS-sparing strategies might reduce the burden associated with SCS-related complications in patients with severe asthma. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Systemic corticosteroids, severe asthma, health care use, dose response, corticosteroid-related complications, cost*

Approximately 5% to 10% of asthmatic patients have severe asthma, which is associated with more asthma-related symptoms and increased risk of exacerbations.[1-3] Because of the higher risk of asthma exacerbations, patients with severe asthma have high asthma-related morbidity.[2,4] Moreover, it has been estimated that health care costs of patients with asthma exacerbations are at least 80% higher than those for patients without exacerbations and that exacerbations are associated with a disproportionate share of health care resource use.[4-6] Severe asthma is difficult to manage, and in 30% to 40% of patients with this condition, it requires regular use of oral corticosteroids.[2,6,7]

It is well established that chronic use of corticosteroids leads to both short- and long-term complications, such as osteoporosis, fractures, susceptibility to infections, obesity, symptomatic coronary artery disease, avascular necrosis, stroke, cataract, glucose metabolism changes, and skin thinning.[8] According to data from the Healthcare Cost and Utilization Project, corticosteroids were the most common cause of drug-related complications, accounting for 10% of such complications and 141,000 hospital stays in the United States in 2004.[9]

However, according to a recent literature review, evidence for the risks and costs associated with systemic corticosteroid (SCS) therapy is sparse and inconsistent, particularly in asthmatic patients.[8] Another review revealed that most studies assessing corticosteroid-related complications are of short duration, thus underestimating the long-term complications associated with SCS use.[10] Moreover, very few studies considered the cumulative dose-response relationship between SCSs and complications, and none of the studies measured the association between the magnitude of SCS exposure and health care resource use.

A longitudinal observational study of Medicaid beneficiaries from 6 states in the United States was performed to evaluate the risk of SCS-related complications by degree of SCS exposure (ie, for patients with higher levels of SCS exposure compared with patients with lower levels of exposure) and to quantify the associated health care costs and resource use among patients with severe asthma.

Abbreviations used

CCI:	Charlson Comorbidity Index
GEE:	Generalized estimating equation
ICD-9-CM:	International Classification of Diseases, Ninth Revision, Clinical Modification
ICS:	Inhaled corticosteroid
OR:	Odds ratio
QIC:	Quasilikelihood under the independence model criterion
SCS:	Systemic corticosteroid

METHODS

Data source

This study used claims data from Medicaid health insurance beneficiaries from 6 US states: Florida (2001-2012), Iowa (1998-2013), Kansas (2001-2013), Missouri (1997-2013), Mississippi (2006-2013), and New Jersey (1997-2013). This data set was chosen because of the long enrollment duration of Medicaid recipients, which permitted observation of both short- and long-term SCS-related complications. Data elements used in the present analysis included information on enrollment history, patient demographic characteristics, date of death, and claims for medical and pharmacy services. Actual costs, which were calculated as the sum of costs reimbursed by Medicaid and patients' out-of-pocket expenses, were also included. The database was deidentified and complied with the Health Insurance Portability and Accountability Act of 1996 to preserve patient anonymity and confidentiality.

Study design and patient selection

A longitudinal, open-cohort, observational study design was used. Eligible patients were 12 years and older, had at least 2 administrative charges associated with a diagnosis of asthma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 493.xx), and had at least 6 months of continuous chronic SCS use (identified by claims for oral, injectable, intravenous, or intramuscular corticosteroids with daily doses of ≥5 mg of prednisone equivalent with no gap of 14 days or more between 2 SCS claims) while being continuously eligible for Medicaid (see Table E1 in this article's Online Repository at www.jacionline.org for the prednisone equivalent dosage of SCSs). These first 6 months constituted the baseline period, and the index date was defined as the first day with a daily dose of at least 5 mg of prednisone equivalent after these first 6 months (see Fig E1 in this article's Online Repository at www.jacionline.org).

Patients with at least 1 claim associated with a diagnosis for any cancer of the respiratory and intrathoracic systems (ICD-9-CM code 160.xx-165.xx) at any time before the index date or at least 1 claim for rheumatoid arthritis (ICD-9-CM code 714.0x, 714.2x), Crohn disease (ICD-9-CM code 555.xx), systemic lupus erythematosus (ICD-9-CM code 710.x0), or multiple sclerosis (ICD-9-CM code 340.xx) at any time in the patient claim history were excluded from the study. These conditions were identified as exclusion criteria because they have SCSs as treatment alternatives and have a similar interlinked relationship of dose and occurrence of SCS-related complications.

The follow-up period of each patient was divided into quarterly time intervals to appropriately account for the fact that a patient's SCS exposure could change over time (with changes in disease state and consequent SCS dose titration). An open-cohort approach was then used to classify quarters of patients' follow-up periods into different degrees of SCS exposure measured based on cumulative SCS dose intensity, as previously reported by Thamer et al[11] (ie, low exposure, ≤6 mg/d; medium exposure, >6-12 mg/d; and high exposure, >12 mg/d). For this analysis, we used the low-exposure group as a reference group.

Outcomes

The study outcomes were the risk of acute and chronic SCS-related complications and associated health care resource use and costs. Acute complications included infections and gastrointestinal complications, and chronic complications included cardiovascular, metabolic, bone- and muscle-related, psychiatric, ocular, skin, adrenal, and other conditions (see Table E2 in this article's Online Repository at www.jacionline.org).

The outcomes were calculated over the follow-up period on a quarterly basis, and health care costs were further annualized. Health care resource use and costs caused by SCS-related complications and grouped into pharmacy dispensings, outpatient visits, emergency department visits, hospitalizations, and other visits were calculated by using (1) medical claims with a diagnosis (ICD-9-CM codes) for SCS-related complications (see Table E2) or (2) pharmacy claims for medications used to treat SCS-related complications (see Table E3 in this article's Online Repository at www.jacionline.org). Costs were adjusted to 2013 US dollars by using the medical care component of the Consumer Price Index.[12]

The power calculation performed during the study protocol development phase indicated that a sample size of 2861 was necessary to achieve 80% power in detecting a 3% effect on health care costs for each additional milligram of increased cumulative daily dose. Whereas the SD of the daily SCS-related complication-associated health care cost was assumed to be twice the expected mean ($4.30), the SD of the mean daily dose was assumed to be 7.5 mg, and the 2-sided α level was set at .05.

Statistical analysis

Descriptive statistics were generated to summarize the patients' baseline characteristics by SCS exposure at the index date. Frequency counts and percentages were used to summarize categorical variables, whereas means, medians, and SDs were used for continuous variables. Baseline characteristics included age, sex, region, race, state, calendar year of index date, pre-existing conditions that can influence the occurrence of SCS-related complications (ie, history of falls, fractures, or diagnosis of osteoporosis; diagnosis of cognitive impairment or depression; diagnosis of epilepsy, cerebrovascular disease or Parkinson disease; diagnosis of diabetes mellitus; and diagnosis of chronic cardiovascular conditions), the Charlson Comorbidity Index (CCI),[13] and all-cause and asthma-related health care costs.

Multivariate generalized estimating equation (GEE) models were used to evaluate the association between SCS exposure and outcomes in patients with medium and high SCS exposure compared with that in patients with low exposure. This approach was chosen to account for the longitudinal and correlated nature of repeated quarterly data for the same patient on SCS exposure and outcomes and for the potential progression of confounders over time. The GEE models controlled for key baseline characteristics (sex, age, race, state, total health care costs, CCI, and ≥1 emergency department or inpatient visit at baseline) and time-dependent variables (quarter of observation, CCI, and cost of concomitant medications).

Odds ratios (ORs), which were estimated with a GEE model by using a binomial distribution with logit link function and exchangeable correlation structure, were used to assess the risk of SCS-related complications assessed as a discrete binary variable for patients with medium and high SCS exposure relative to that of patients with low SCS exposure. The GEE model used to estimate incidence rate ratios, CIs, and P values of health care resource use because of SCS-related complications was based on a Poisson distribution with an independent correlation structure to account for the discrete nature of health care resource use event counts. Adjusted cost differences between patients with medium/high SCS exposure and patients with low SCS exposure were assessed with a GEE model by using a normal distribution with exchangeable correlation structure to account for the continuous nature of costs. In addition to the aforementioned key baseline characteristics and time-dependent variables, the GEE models controlled for the year of index date and presence of a SCS-related complication of interest or pre-existing condition at baseline, where applicable. Nonparametric bootstrap procedures with 999 replications were used to estimate 95% CIs and P values.

All analyses were conducted with SAS software, version 9.3, of the SAS System for Windows (SAS Institute, Cary, NC). The SAS "PROC GENMOD" procedure was used to conduct the GEE regressions and to calculate the quasilikelihood under the independence model criterion (QIC) measures