Corticosteroid-related toxicity in patients with chronic idiopathic urticaria–chronic spontaneous urticaria

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ABSTRACT

Background: *Treatments for patients with chronic idiopathic urticaria (CIU)–chronic spontaneous urticaria (CSU) who were unresponsive to antihistamines include oral corticosteroids (OCS). Risks of OCS-related side effects in these patients have not been described quantitatively.*

Objective: *To investigate the relationship between OCS use and the risk of developing side effects possibly attributable to OCS and associated health care costs in privately insured patients with CIU/CSU.*

Methods: *This retrospective cohort study analyzed a commercial claims data base from January 1, 2008, to December 31, 2012. Patients with CIU/CSU were identified by International Classification of Diseases, Ninth Revision, Clinical Modification codes* via *a validated algorithm. Possible OCS-related side effects included the following: diabetes mellitus, hypertension, lipid disorders, cataracts, depression or mania, osteoporosis or fractures, and infectious diseases. A time-dependent Cox regression (adjusted for age, sex, Charlson Comorbidity Index, and immunomodulator use) was used to separately model cumulative oral prednisone-equivalent exposure and the risk of side effects. Incremental total adjusted health care costs were compared in patients with versus patients without possible OCS-related side effects.*

Results: *Among 12,647 patients with CIU/CSU, 55.4% used OCS. An additional 1 g of prednisone-equivalent exposure was associated with a 7% increase in the likelihood of developing a possible side effect (hazard ratio, 1.07 [95% confidence interval, 1.05–1.08]). From the period before to the period after OCS initiation, the total mean adjusted annual health care costs increased by $1833 in users of OCS with new possible side effects and decreased by $2183 in patients without new possible side effects ($p < 0.001$).*

Conclusion: *Patients with CIU/CSU who were treated with OCS had an increased risk of possible OCS-related side effects and higher total health care costs than their counterparts not treated with OCS.*

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Chronic idiopathic urticaria (CIU)–chronic spontaneous urticaria (CSU) is a systemic condition characterized by pruritus, hives, and, occasionally, angioedema. It recurs daily or almost daily for at least 6 weeks without an identifiable cause.[1,2] CIU/CSU may impose a substantial burden on health-related quality of life, with impairment similar to that of patients with ischemic heart disease.[3] For patients with CIU/CSU, U.S.[1] and European[2] guidelines recommend initial treatment with a nonsedating H_1 antihistamine. Both guidelines advise that patients with CIU/CSU still symptomatic while on H_1 antihistamines have several treatment alternatives, including a short course (typically ≤10 days) of oral corticosteroids (OCS). Topical steroid preparations are not generally helpful for patients with CIU/CSU, although topical anti-itch preparations may be useful. The guidelines advise against the long-term use of OCS because the associated side effects usually lead to negative health outcomes.[1,2]

Oral formulations of corticosteroids present an inexpensive treatment option for many clinical conditions with a known or presumed inflammatory component.[4] Although the clinical community often relies on the shortest course of corticosteroid treatment, urticaria may flare when treatment is discontinued, which necessitates additional courses. Repeated short courses are challenging to track, and side effects of systemic corticosteroids increase with continual or intermittent

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use. Patients who receive long-term corticosteroids may experience side effects of cardiovascular disease and dyslipidemia, cataracts and glaucoma, gastrointestinal events, hyperglycemia and diabetes mellitus, immunosuppression, myopathy, osteoporosis and fractures, psychiatric disturbances (including dysphoria and emotional lability), sleep disturbances, suppression of the hypothalamic-pituitary axis, thinning of the skin with bruising, and weight gain and fat redistribution.[4] Therefore, despite its low direct costs, OCS treatment may increase overall health care costs, which result from the added costs of treatments for side effects.

In this context, it is important for the health policy and for the scientific and clinical communities to understand the specific risks of developing OCS-related side effects and the costs that may be associated with these side effects, particularly when selecting therapies for a chronic condition such as CIU/CSU. Unfortunately, quantitative data on the incidence of side effects and costs associated with OCS use in patients with CIU/CSU have not been well elucidated. The aim of this study was to examine the relationship between OCS use and the risk of developing side effects possibly attributed to corticosteroid use in privately insured patients with CIU/CSU. Furthermore, an analysis quantified the potential health care costs associated with these side effects.

METHODS

The specific research questions pursued were the following: (1) to what extent is OCS treatment associated with the increase in possible OCS-related side effects among patients with CIU/CSU who are enrolled in commercial U.S. health plans; and (2) in the event of occurrence of possible OCS-related side effects in the above-mentioned population, was this occurrence associated with any change in health care costs? To answer these questions, we studied a cohort of patients with CIU/CSU (including patients who were exposed to OCS and those who were not) to understand the costs associated with OCS use and possible side effects. Within users of OCS, we compared the overall rate of health care resource use and costs between those who had possible side effects and those who did not have possible OCS-related side effects.

Data

This retrospective cohort study used a Health Insurance Portability and Accountability Act–compliant administrative claims data base. The data base includes detailed deidentified information on inpatient admissions, outpatient encounters, prescription drug claims, and enrollment data for >13 million patients annually. The data are derived from medical and pharmacy claims from multiple health plans and are broadly representative of the U.S. commercially insured population. The data were from January 1, 2008, through December 31, 2012, which thus comprised four calendar years (2008, 2009, 2010, 2011). Data were linkable at the patient level. Because the data base did not contain protected health information, the study was exempt from review by a human subject protection committee.

Study Population

We used a validated algorithm[5] to identify patients with CIU/CSU who met one of the following criteria based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: (1) two outpatient diagnoses (in any combination) among the following: 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), or 708.9 (urticaria, unspecified) at least 6 weeks apart in a calendar year; or (2) one outpatient diagnosis of 708.1, 708.8, or 708.9 plus one diagnosis of 995.1 (nonhereditary angioedema) at least 6 weeks distant from the 708.x diagnosis in a calendar year. This algorithm demonstrated a positive predictive value of 90.4% and a sensitivity of 71.1%.[5] Patients who met either criterion 1 or 2 were classified as having CIU/CSU. The year of identification was labeled as the baseline period. January 1 of the year after the baseline period was labeled as the index date, and the subsequent period was labeled as the study period. For example, for patients identified in year 2008, the index date was defined as January 1, 2009. For the patients identified in multiple calendar years, the earliest index date was used. We excluded patients who were younger than 18 years of age at the end of the baseline year and patients whose continuous enrollment with the health plan lasted <12 months before and after the index date. Patients were followed up from the index date for at least 1 year, until the end of enrollment or study end (January 31, 2012). OCS exposure was evaluated throughout both the baseline and study periods. The incidence of possible side effects was evaluated in the postindex period only.

Study Variables

OCS use, described by cumulative prednisone-equivalent exposure,[6] was calculated on a daily basis throughout the baseline and study periods. The main outcome of interest was the risk of developing a possible OCS-related side effect. We identified possible side effects in the following way. First, we reviewed the literature to identify a list of side effects reported to be associated with corticosteroid therapy.[7] Second, three physicians reviewed the list and excluded events (Supplemental Table 1) that were likely to be poorly identifiable in the claims data, not identifiable in the

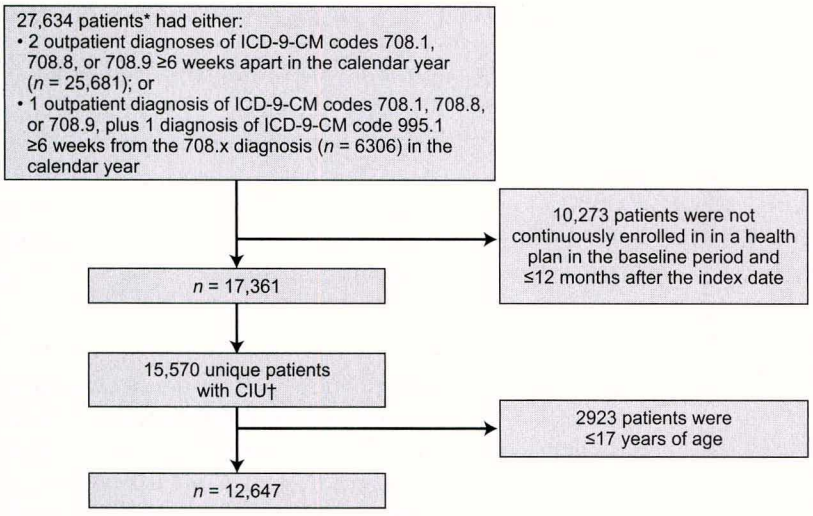

Figure 1. *Patient disposition. *Some patients were identified in >1 calendar year. †For patients identified in multiple calendar years, the earliest year was used. ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; CIU = chronic idiopathic urticaria.*

Table 1 **Baseline patient demographics**

Characteristic	All Patients with CIU/CSU (*N* = 12,647)	Patients with CIU/CSU with OCS Use (*n* = 7009)*	Patients with CIU/CSU without OCS Use (*n* = 5638)*
Age, mean ± SD, y	49.2 ± 15.9	49.2 ± 15.4	49.3 ± 16.5
95% CI	48.9–49.5	48.8–49.5	48.8–49.7
Female, no. (%)	8979 (71.0)	5042 (71.9)	3937 (69.8)
Baseline year, no. (%)			
2008	3434 (27.2)	1832 (26.1)	1602 (28.4)
2009	3024 (23.9)	1639 (23.4)	1385 (24.6)
2010	3020 (23.9)	1698 (24.2)	1322 (23.4)
2011	3169 (25.1)	1840 (26.3)	1329 (23.6)
Follow-up, mean ± SD, days	756.3 ± 378.9	749.6 ± 377.0	764.6 ± 381.2
95% CI	749.7–762.9	740.8–758.4	754.6–774.5
CCI score, mean ± SD	0.90 ± 1.54	0.95 ± 1.54	0.85 ± 1.53
95% CI	0.88–0.93	0.91–0.98	0.81–0.89
No. chronic conditions, mean ± SD	3.38 ± 2.12	3.49 ± 2.18	3.23 ± 2.05
95% CI	3.34–3.41	3.44–3.55	3.17–3.28

CIU = Chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; OCS = oral corticosteroid; SD = standard deviation; CI = confidence interval; CCI = Charlson Comorbidity Index.
**In the baseline period.*

study population, or otherwise inappropriate for this study, which left the following primary conditions of interest: diabetes mellitus, hypertension, lipid disorders,[8] cataracts, neuropsychiatric conditions (depression[9,10] or mania), skeletal conditions (vertebral or nonvertebral fractures or osteoporosis), and infectious diseases (pneumonia or opportunistic infections, including herpes zoster). We included obesity as an exploratory condition because it was an outcome of interest but not well coded.

We identified the primary and exploratory conditions in the data base through ICD-9-CM and Current Procedural Terminology codes listed in claims with the selected procedure or diagnosis in any coding field. We ensured that possible side effects occurred after OCS exposure in the following way. Chronic conditions (diabetes mellitus, hypertension, lipid disorders, cataracts, depression, mania, osteoporosis, obesity, angina pectoris, chronic heart disease, hypertensive heart disease, and peripheral and cerebrovascular disease) were coded as possible side effects only if claims for them occurred in the study period and not in the baseline period. Conditions of an acute nature, defined as any event that occurred in the follow-up period, were

coded as possible side effects if claims for them occurred in the study period. Because nonvertebral fractures may heal during an extended period of time, a fracture was coded as a possible side effect if no fracture-related claim occurred at least 60 days before the index date (so the fracture would not precede OCS exposure or overlap with it). We also compared annual incremental total health care costs from baseline to the postindex period in patients with versus those without possible side effects.

Statistical Analyses

We described patient demographics and medication use (including OCS use) in the baseline period. The estimated, unadjusted rate (per 100 patient-years) of occurrence of any of the primary side effects (combined) and of each possible side effect (primary or exploratory) were calculated separately. To study the relationship between OCS exposure and possible side effects, Cox proportional hazard models were used, with OCS use as a time-dependent variable. The statistical model provided hazard ratios (HR) associated with any possible side effect and each individual possible side effect separately. To control for the imbalances between the groups, all the estimates were adjusted for age, sex, Charlson Comorbidity Index (CCI) score, and use of immunosuppressive and miscellaneous agents (cyclosporine, dapsone, doxepin, hydroxychloroquine, methotrexate, mycophenolate, and sulfasalazine). The CCI is used to predict 1-year mortality for 22 possible comorbid conditions.[11] The adjusted HRs and their 95% confidence intervals (CI) were estimated for the association between OCS exposure and the risk of possible side effects. Incremental annual costs (from the baseline period to the study period) were compared between the groups with versus those without possible side effects. Adjustment for imbalances between the groups was performed with linear regression models adjusted by age, sex, CCI score, and use of immunosuppressive or miscellaneous agents. All data transformations and statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All the tests were two-sided, with a significance level of 0.05.

RESULTS

Patient Characteristics

The data base search identified 12,647 patients with CIU/CSU (Fig. 1). Overall, the patients had a mean age of 49.2 years (95% CI, 48.9–49.5 years), median of 49 years, and range of 18–83 years; most (71.0%) were women (Table 1). The patients who used OCS during the baseline period were similar to their counterparts who did not use OCS with respect to age, sex, and the number of chronic conditions. The baseline CCI score of users of OCS exceeded that of those without baseline OCS use (0.95 versus 0.85, respectively; $p < 0.001$).

Table 2 **Baseline CIU/CSU medication use**

Medications	Patients with CIU/CSU, no. (%) (N = 12,647)
Prescription antihistamines*	5793 (45.8)
Second- and third-generation H_1 antihistamines	4724 (37.4)
Other H_1 antihistamines (all others)	898 (7.1)
H_2 antihistamines	1184 (9.4)
Oral corticosteroids	7008 (55.4)
Leukotriene modifiers#	1887 (14.9)
Immunosuppressive agents§	309 (2.4)
Miscellaneous agents¶	1685 (13.3)
Omalizumab	37 (0.3)

CIU = Chronic idiopathic urticaria; CSU = chronic spontaneous urticaria.
**Over-the-counter medications were not included in the data base.*
#Montelukast, zafirlukast, or zileuton.
§Cyclosporine, methotrexate, or mycophenolate.
¶Dapsone, doxepin, hydroxychloroquine, or sulfasalazine.

Baseline CIU/CSU Medication Use

During the baseline period, 45.8% of patients filled antihistamine prescriptions (mostly second- or third-generation H_1 antihistamines), and 55.4% of the patients used OCS (Table 2). OCS exposure lasted a mean of 16.2 days (95% CI, 15.6–16.9 days) among all the patients, and the mean total prednisone-equivalent dose exposure totaled 0.368 g (95% CI, 0.354–0.381 g), median of 0.105 g, and range of 0.0–27.5 g. Among users of OCS, baseline period OCS exposure lasted a mean of 29.3 days (95% CI, 28.3–30.3 days); the mean prednisone-equivalent dose exposure totaled 0.663 g (95% CI, 0.640–0.686 g), median of 0.400 g, and range of 0.007–27.5 g.

Outcomes of Interest

During the baseline period, 58.5% of the patients experienced at least one of the studied primary possible side effects (data not shown). The frequency of individual primary possible side effects was identified for the primary conditions of interest: lipid disorder (37.0%), hypertension (34.1%), diabetes (11.7%), neuropsychiatric conditions (11.5%), cataract (8.4%), skeletal conditions (6.8%), and infectious diseases (2.8%). In patients with baseline OCS exposure (at any dose), the unadjusted probability of a new occurrence of the fol-

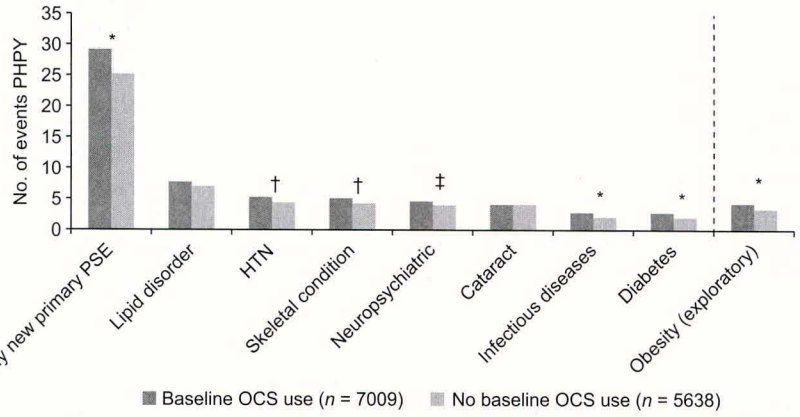

Figure 2. *Unadjusted possible side effects per 100 patient-years (PHPY). Possible side effects were identified by using International Classification of Diseases, Ninth Revision, Clinical Modification and the Current Procedural Terminology codes. For patients with events of interest, patient-years were the years from the index date to the event. For patients without events of interest, patient-years were the years from the index date to the end of follow-up. The p values indicate comparisons between the baseline period OCS exposure and no baseline period OCS exposure groups. *$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$. HTN = Hypertension; OCS = oral corticosteroid.*

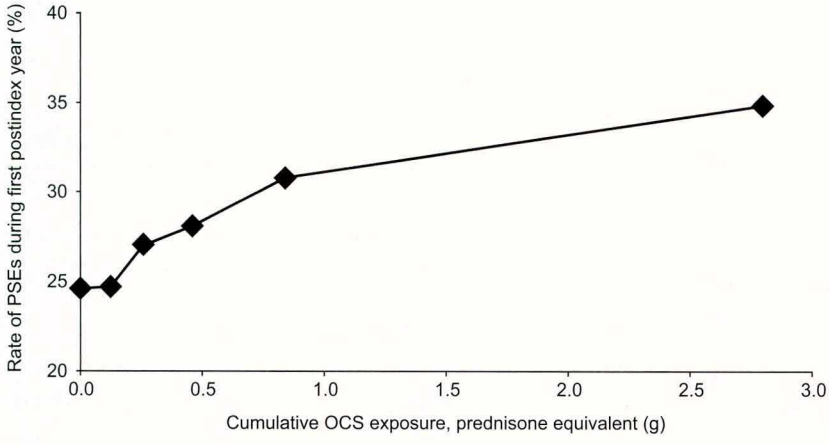

Figure 3. *The unadjusted rate of possible side effects (PSE) by prednisone-equivalent oral corticosteroid (OCS) exposure during the baseline period. The prednisone equivalence was calculated as per published source (from Ref. 5).*

lowing possible side effects was statistically significantly higher than in those without baseline OCS exposure: hypertension, skeletal conditions, neuropsychiatric conditions, infectious diseases, diabetes, and obesity (Fig. 2). The unadjusted rate of a new possible side effect (for any of the primary events combined) was 27.3 per 100 patient-years.

In the study period, as prednisone-equivalent OCS exposure increased, so did the risk of developing a possible side effect (Fig. 3). When controlled for potential confounders during the entire postindex period, 1 g of prednisone-equivalent OCS exposure was associated with an increased likelihood of any possible side effects combined (HR 1.07 [95% CI, 1.05–1.08]). Similarly, 1 g of prednisone-equivalent exposure was associated with individual events that yielded the following increased HRs: diabetes (HR 1.07 [95% CI, 1.04–1.10]), hypertension (HR 1.05 [95% CI, 1.01–1.08]), neuropsychiatric conditions (HR 1.05 [95% CI, 1.02–1.08]), skeletal conditions (HR 1.08 [95% CI, 1.06–1.11]), infectious diseases (HR 1.07 [95% CI, 1.05–1.10]), and obesity (HR 1.05 [95% CI, 1.02–1.08]) (Table 3).

Health Care Costs

In both the baseline and postindex periods, the unadjusted annual health care costs were higher in patients with claims than in patients without such claims, which indicated possible side effects associated with OCS use (Table 4). From the baseline period to the postindex period, the mean unadjusted total health care costs decreased in patients without possible OCS-related side effects (−$2050 [95% CI, −$2567 to −$1534]) and increased in their counterparts with such side effects ($1636 [95% CI, $651–$2622]). The adjusted incremental annualized health care costs followed the same pattern (Fig. 4): −$2183 (95% CI, −$1528 to −$2837) versus $1833 ($1033–$2636), $p < 0.0001$.

DISCUSSION

The analysis revealed frequent use of OCS in patients with CIU/CSU, with more than half of the patients

Table 3 **Adjusted HRs (95% CI) per additional 1 g of cumulative oral corticosteroid (prednisone-equivalent) exposure**

Possible Side Effect	HR (95% CI)*	*p* Value
Combined primary possible side effects		
First primary possible side effect	1.07 (1.05–1.08)	<0.001
Primary possible side effect		
Diabetes mellitus	1.07 (1.04–1.10)	<0.001
Hypertension	1.05 (1.01–1.08)	0.004
Lipid disorders	1.03 (1.00–1.06)	0.049
Cataract	1.02 (0.98–1.05)	0.318
Neuropsychiatric conditions	1.05 (1.02–1.08)	0.001
Skeletal conditions	1.08 (1.06–1.11)	<0.001
Infectious diseases	1.07 (1.05–1.10)	<0.001
Exploratory end point		
Obesity	1.05 (1.02–1.08)	<0.001

HR = Hazard ratio; CI = confidence interval.

**Risks adjusted for age, sex, Charlson Comorbidity Index, and the use of immunosuppressive or miscellaneous agents (cyclosporine, mycophenolate, methotrexate, doxepin, dapsone, hydroxychloroquine, and sulfasalazine); prednisone equivalence was calculated as per published source (from Ref. 5).*

Table 4 **Total and incremental annual health care costs* stratified by any possible side effect**

	All Patients with CIU/CSU (N = 12,647)	Without Primary Possible Side Effect (n = 7563)	With Primary Possible Side Effect (n = 5084)
Annualized total costs, 1-y preindex period, mean ± SD	$13,023 ± $27,183	$10,766 ± $20,913	$16,366 ± $34,191
95% CI	$12,550–$13,497	$10,305–$11,248	$15,426–$17,306
Annualized total costs, postindex period, mean ± SD	$12,455 ± $28,209	$8726 ± $19,845	$18,002 ± $36,639
95% CI	$11,963–$12,947	$8279–$9174	$16,995–$19,010
Incremental annualized total costs (difference between post- and preindex periods), mean ± SD	−$568 ± $28,872	−$2050 ± $22,921#	$1636 ± $35,835#
95% CI	−$1072 to −65	−$2,567 to −1534	$651–$2622

CIU = Chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; SD = standard deviation; CI = confidence interval.

**Annualized costs in the postindex period minus the costs in the 1-year preindex period. All costs were converted into 2012 U.S. dollars by using the medical care components of the Consumer Price Index.*

#$p < 0.001$ for the patients with primary possible side effect vs the patients with no primary possible side effect.

filling prescriptions for OCS. Frequent use of OCS in patients with CIU/CSU also has been reported in another claims-based analysis at 53.7%, with a mean ± SD supply of 29.7 ± 52.2 days.[12] In the current study, filling prescriptions for OCS was associated with possible side effects of OCS use. OCS-related side effects have been reported in other inflammatory conditions in which OCS have been frequently used, such as rheumatoid arthritis,[13,14] inflammatory bowel disease,[15–18] asthma,[19–23] and chronic obstructive pulmonary disease.[24–26] The analysis indicates that, any given point in time, with all other factors being equal, a person with one additional gram of prednisone-equivalent OCS would face a 7% higher likelihood of developing any of the studied possible side effects than a similar individual without that additional gram of exposure. Likewise, a person with two additional grams of prednisone-equivalent OCS would face a 14% higher likelihood of the same outcomes than a similar individual without OCS exposure.

OCS are recommended in patients with CIU/CSU if H_1 or H_2 antihistamines and, possibly, leukotriene

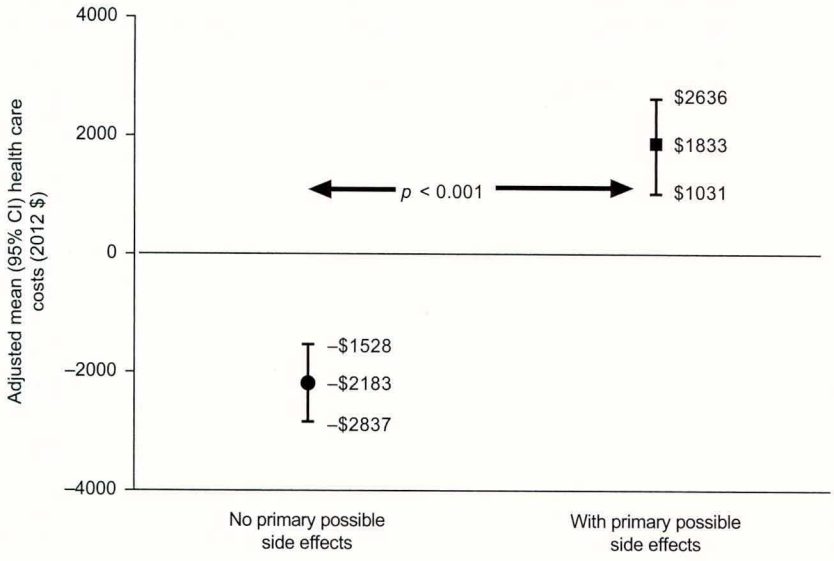

Figure 4. *Adjusted* incremental annual health care costs.† *Adjusted by age, sex, Charlson Comorbidity Index score, and immunomodulator use by using a linear regression model. †Annualized costs in the postindex period minus the costs in the 1-year pre-index period. CI = Confidence interval.*

modifiers failed, but there is some discretion as to where and how often OCS should be used relative to other available therapies.[1,2] The direct and immediate cost of OCS treatment is relatively low; therefore, elucidating its long-term costs and outcomes is critical. This study demonstrated that, in addition to its effect on quality of life, the use of OCS was associated with increased health care costs. OCS treatment presented a seemingly inexpensive treatment option associated with low acquisition costs and low copays for the patient. The current analyses were consistent with conclusions from research in other disease areas indicating that side effects of OCS may lead to a substantial increase in overall costs above and beyond the direct costs of OCS.[27]

The costs in the group without possible side effects decreased from the baseline period to the study period. The studied data base provided no explanation as to why this happened; however, we hypothesized that this may be a phenomenon of regression to the mean. Because the algorithm defined CIU/CSU based on urticaria-related health care events, the patients selected for this study were likely to have a more active condition during the baseline period than in other years. Spontaneous resolution of chronic urticaria occurs in up to half of patients within the first year, and after 5 years ~80% are symptom free.[28] It is possible that it is the resolution of urticaria in some of the cohort that is responsible for the cost reduction.

These results should be interpreted taking account of the study's limitations. The effects of confounding factors, such as differences in the severity of CIU/CSU, could not be fully controlled. Variables that were not available in the claims that may be important to understand CIU/CSU outcomes include the use of other medications, such as over-the-counter antihistamines. However, the possible side effects related to the use of OCS for which costs were analyzed, such as diabetes and hypertension, would not generally be expected to result from higher CIU/CSU severity in the absence of OCS usage.[1,2] Thus, confounding by indication is a less likely explanation for the observed findings. Underestimation of costs was likely because only direct costs of possible side effects related to the use of OCS were included.

Another limitation of the analyses is that medical record confirmation of a CIU/CSU diagnosis was not possible, nor is there a single ICD-9-CM code specific to CIU/CSU. However, we used a validated algorithm previously demonstrated to be accurate in identifying patients with CIU/CSU.[5] The algorithm had a positive predictive value of 90.4% and a sensitivity of 71.1%. There is no agreed-on standard for adequate sensitivity. In a study of >4000 subjects, sensitivity of ICD-9-CM codes for chart review–validated conditions ranged from 9% for weight loss to 83% for metastatic cancer, the median value was 46%, and the mean value was 49%.[29] Other studies found similar ranges, which made the sensitivity of our algorithm at the upper end of accuracy.[30,31]

CONCLUSION

OCS use was common in patients with CIU/CSU in this data base; more than half of the patients with CIU/CSU followed up for ≥12 months used OCS. Exposure to OCS was associated with an increased risk of possible side effects, including hypertension, skeletal conditions, neuropsychiatric conditions, infectious diseases, diabetes, and obesity, as well as all possible side effects combined, and increased with increasing cumulative prednisone-equivalent OCS exposure. Use of OCS was associated with increased health care costs.

Disease-modifying therapies that minimize the use of OCS remain a research focus in CIU/CSU.

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