Corticosteroid-Related Adverse Events in Chronic Idiopathic Urticaria

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INTRODUCTION

- Oral corticosteroids (OCS) are a common therapy in patients with chronic idiopathic urticaria (CIU) who remain symptomatic on H_1-antihistamine therapy.[1]
- OCS are associated with adverse events (AEs) that may lead to negative health outcomes.[2,3]
- Data on quantitative risks of AEs associated with OCS in patients with CIU are lacking.

OBJECTIVES

- To study baseline OCS use among patients with CIU.
- To determine the extent to which the use of OCS in patients with CIU increases the risk of developing corticosteroid-related AEs.

METHODS

Study Population

- Data from a commercial claims database were used for this study (January 1, 2008–December 31, 2012, inclusive).
- Patients were identified in calendar years 2008–2011 (identification period). We included patients with CIU who met the following criteria during a single calendar year.
- Inclusion criteria:
  - 2 outpatient diagnoses of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 708.1, 708.8, or 708.9 (idiopathic urticaria, other specified urticaria, and unspecified urticaria, respectively) ≥6 weeks apart in the calendar year; or
  - 1 outpatient diagnosis of 708.1, 708.8, or 708.9, plus 1 diagnosis of ICD-9-CM code 995.1 (nonhereditary angioedema) ≥6 weeks from the 708.x diagnosis in the calendar year.
- Exclusion criteria:
  - Not continuously enrolled in a health plan in the baseline period and ≤12 months after the index date; or
  - <18 years of age at the end of the baseline period.
- The index date of identified patients was defined as January 1 of the next calendar year.
- For patients who were identified in multiple calendar years, the earliest index date was used.
- The baseline period was defined as 1 year immediately before the index date. The follow-up period began on the index date and continued for ≥1 year until the end of enrollment or study end (December 31, 2012).

Study Outcomes

- The main outcome of interest was the risk of developing a new instance of a possible AE.
  - Possible AEs were identified based on ICD-9-CM and Current Procedural Terminology codes listed in the claims with the selected procedure or diagnosis in any coding field.
- Conditions of interest included the following:
  - Primary conditions: lipid disorders,[4] hypertension, skeletal conditions (nonvertebral/vertebral fractures, osteoporosis), neuropsychiatric conditions (depression,[5,6] mania), cataracts, infectious diseases (pneumonia, opportunistic infections including herpes zoster), diabetes; and
  - Exploratory condition: obesity.
- New instances of a possible AE were identified in the following ways:
  - Chronic conditions: a condition appearing in the follow-up period but not in the baseline period; and
  - Acute conditions: any event occurring in the follow-up period was considered an isolated event.
- OCS use, described by cumulative prednisone-equivalent exposure,[7] was calculated on a daily basis throughout the baseline and follow-up periods. This measure was included as a time-dependent variable in the models. Parenterally administered corticosteroids were excluded from this analysis.

Statistical Analyses

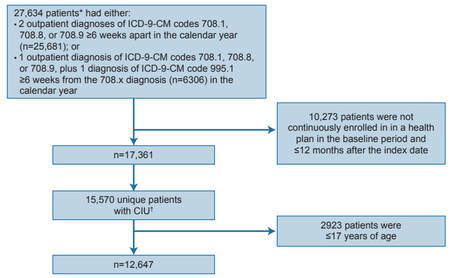
- OCS use in the baseline period was estimated for all patients.
- The unadjusted rate per 100 patient-years was estimated for any primary possible AE and each possible AE separately.
- The adjusted hazard ratios and their 95% confidence intervals were reported for the association between OCS exposure and the risk of possible AEs for any new possible AE and for each individual possible AE (primary or exploratory).
- A time-dependent Cox regression (proportional hazards) model was used to study the association between possible AE risk and daily level OCS use.
  - Separate models were conducted for the first new possible AE and each individual possible AE as dependent variables.
  - To control for baseline differences, all risks 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).

RESULTS

Patient Characteristics

- 12,647 patients were included in the cohort (**Figure 1**). The mean (SD) age was 49.2 (15.9) years (median, 49 [range, 18–83] years) and 71.0% were female (**Table 1**).

Figure 1. Patient Disposition



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

Table 1. Baseline Patient Demographics

Characteristic	All Patients With CIU n=12,647	Patients With CIU (OCS*) n=7009	Patients With CIU (No OCS*) n=5638
Mean (SD) age, y	49.2 (15.9)	49.2 (15.4)	49.3 (16.5)
Female, n (%)	8979 (71.0)	5042 (71.9)	3937 (69.8)
Baseline year, n (%)			
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)
Mean (SD) days of follow-up	756.3 (378.9)	749.6 (377.0)	764.6 (381.2)
Mean (SD) CCI score	0.90 (1.54)	0.95 (1.54)	0.85 (1.53)
Mean (SD) no. of chronic conditions	3.38 (2.12)	3.49 (2.18)	3.23 (2.05)

CCI, Charlson Comorbidity Index; CIU, chronic idiopathic urticaria; OCS, oral corticosteroids. *In the baseline period.

- Allergic rhinitis was noted in 43.8% of the cohort.

CIU Medication Use: Baseline Period

- In the baseline period, 45.8% of patients used prescription antihistamines (most commonly second- or third-generation H_1-antihistamines) and 55.4% used OCS (**Table 2**).
- In the baseline period, the mean (SD) number of OCS supply days was 16.2 (36.0) and mean (SD) total prednisone-equivalent OCS (PE-OCS) dose exposure was 0.367 (0.799) g.

Table 2. CIU Medication Use in the Baseline Period

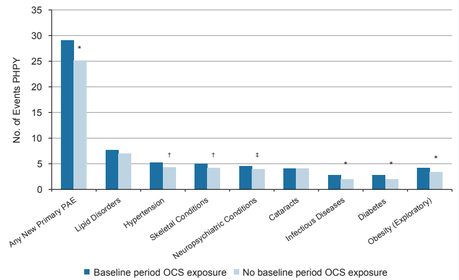
Medications	Patients With CIU, n (%) n=12,647
Prescription antihistamines*	5793 (45.8)
Second- and third-generation H_1-antihistamines	4724 (37.4)
All other H_1-antihistamines	898 (7.1)
H_2-antihistamines	1184 (9.4)
OCS	7008 (55.4)
Leukotriene receptor modifiers (montelukast, zafirlukast, zileuton)	1887 (14.9)
Immunosuppressive agents (cyclosporine, methotrexate, mycophenolate)	309 (2.4)
Miscellaneous agents (dapsone, doxepin, hydroxychloroquine, sulfasalazine)	1685 (13.3)
Omalizumab	37 (0.3)

CIU, chronic idiopathic urticaria; OCS, oral corticosteroids. *Only prescription antihistamines were evaluated; Over-the-counter medications were not available in the database.

AEs of Interest

- 58.5% of patients had ≥1 primary possible AE(s) of interest in the baseline period.
  - Lipid disorder was the most common (37.0%).
  - Infectious diseases were the least common (2.8%).
- The rate of new primary possible AEs was 27.3 per 100 patient-years.
- OCS use in the baseline period was associated with an increase in the unadjusted risk of all studied primary possible AEs combined and with an increased risk of the following individual possible AEs: hypertension, skeletal conditions, neuropsychiatric conditions, infectious diseases, diabetes, and obesity (**Figure 2**).

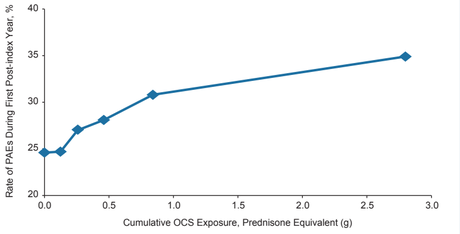
Figure 2. Unadjusted PAEs PHPY, Stratified by OCS Use in the Baseline Period



OCS, oral corticosteroids; PAE, possible adverse event; PHPY, per 100 patient-years. For patients with events of interest, person-years were the years from the index date to the event. For patients without events of interest, person-years were the years from the index date to the end of follow-up. *P* values indicate comparison between the baseline period OCS exposure and no baseline period OCS exposure groups. *$P<0.001$; †$P<0.01$; ‡$P<0.05$.

- In the first post-index year, as PE-OCS exposure increased, so did the risk of developing a primary possible AE (**Figure 3**).

Figure 3. Unadjusted Rate of PAEs by PE-OCS Exposure During the Baseline Period



OCS, oral corticosteroids; PAE, possible adverse event; PE-OCS, prednisone-equivalent oral corticosteroid.

- When adjusted for age, sex, CCI score, and use of immunosuppressive and miscellaneous agents, OCS exposure during the baseline period was associated with a risk of hypertension, skeletal conditions, neuropsychiatric conditions, infectious diseases, diabetes, and obesity (**Table 3**).
  - At any given point in time, all else being equal, a person with 1 additional gram of PE-OCS would face a 7% higher likelihood of developing any of the studied possible AEs than a similar individual without that additional gram of exposure. Similarly, a person with 2 additional grams of PE-OCS would face a 14% higher likelihood of the same outcomes than a similar individual without that exposure.

Table 3. Adjusted HRs (95% CI) per Additional 1 g Cumulative PE-OCS Exposure

PAE	HR (95% CI)*	*P* Value
Combined primary PAE		
First primary PAE	1.07 (1.05–1.08)	<0.001
Individual primary PAE		
Lipid disorders	1.03 (1.00–1.06)	0.049
Hypertension	1.05 (1.01–1.08)	0.004
Skeletal conditions	1.08 (1.06–1.11)	<0.001
Neuropsychiatric conditions	1.05 (1.02–1.08)	0.001
Cataracts	1.02 (0.98–1.05)	0.318
Infectious diseases	1.07 (1.05–1.10)	<0.001
Diabetes	1.07 (1.04–1.10)	<0.001
Individual exploratory endpoint		
Obesity	1.05 (1.02–1.08)	<0.001

CI, confidence interval; HR, hazard ratio; PAE, possible adverse event; PE-OCS, prednisone-equivalent oral corticosteroid. *Risks adjusted for age, sex, Charlson Comorbidity Index score, and use of immunosuppressive and miscellaneous agents (cyclosporine, mycophenolate, methotrexate, doxepin, dapsone, hydroxychloroquine, and sulfasalazine).

CONCLUSIONS

- OCS treatment was used in >50% of patients with CIU followed for ≥12 months.
- OCS exposure was associated with an increased risk of any primary possible AEs when combined, and the same was true for the following possible AEs individually: hypertension, skeletal conditions, neuropsychiatric conditions, infectious diseases, diabetes, and obesity (exploratory).
  - The risk of possible AEs increased with increasing cumulative PE-OCS exposure (7%/gram prednisone equivalent).

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