Incidence of Churg-Strauss Syndrome in Asthma Drug Users: A Population-Based Perspective

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ABSTRACT. ***Objective.*** To estimate the incidence of Churg-Strauss syndrome (CSS) among a large population of asthma drug users.

Methods. A retrospective study was conducted among patients who had been dispensed asthma drugs at 3 managed care organizations. Adults who received ≥ 3 dispensings of an asthma drug during any consecutive 12-month period between January 1, 1995 and June 30, 2000 were identified. Information on patient age, gender, enrollment status, asthma drugs dispensed, and inpatient and outpatient diagnoses and procedures was obtained from automated databases. Chart reviews were performed on persons identified by combinations of diagnostic and billing codes indicative of CSS. A rheumatologist reviewed abstracted information on all subjects; those who met ≥ 2 American College of Rheumatology criteria for CSS were reviewed by 2 clinical experts. Each clinical expert independently rated the cases; disagreements were resolved by consensus. Cases classified as having "probable/definite" CSS were included in these analyses. The incidence of CSS was estimated overall and according to patient gender, age, and calendar year.

Results. From a population of 184,667 asthma drug users contributing 606,184 person-years of exposure, 21 incident cases of CSS were identified (overall incidence of 34.6 per million person-years; 95% confidence interval 21.4 to 53.0). Incidence rates did not differ by gender and age group. The incidence rates for 1995, 1996, 1997, 1998, 1999, and the first 6 months of 2000 were 0, 22, 52, 75, 14, and 14 per million person-years respectively.

Conclusions. Results from this population-based study suggest a somewhat lower incidence of CSS in asthma drug users than previously reported and provides important information as to the risk of developing CSS from a population-based perspective. (J Rheumatol 2005;32:1076–80)

Key Indexing Terms:
CHURG-STRAUSS SYNDROME
INCIDENCE
AUTOMATED DATA
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Churg-Strauss syndrome (CSS) is a rare systemic vasculitis characterized by hypereosinophilia, asthma, allergic rhinoconjunctivitis, and sinusitis. There is limited information on the epidemiology of the condition from a population-based perspective. Using information from regional hospitals where patients are referred by their primary care physicians and subsequently identified as having CSS in the United Kingdom, Spain and Norway, the annual incidence of the CSS has been estimated to be between 0.5-3.1 per million; these estimates were based upon 14, 2, and 2 cases respectively from each site[1,2]. Recent studies have suggested that the incidence of CSS may be increasing. In a defined, ethnically homogeneous population of approximately 500,000 in an eastern coastal region of the United Kingdom,

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the incidence of CSS was 1.5 per million between 1988 and 1992, while it was 3.7 per million between 1993 and 1997[3]. This represents a 2.5-fold increase[3,4]. Whether these temporal trends represent true increases in CSS incidence or increased physician awareness of the condition is uncertain[2,4]. There have also been reports of CSS in relation to treatment with specific asthma drug therapies[5-10].

The incidence and prevalence of CSS in an asthmatic population is much higher than in the general non-asthmatic population[11]. In the United States, the annual incidence rate of CSS among patients with asthma using leukotriene modifiers (both zafirlukast and montelukast) was reported to be approximately 60 per million based on data from specialty referral hospitals and case reports[11]. Using a database in the United Kingdom which contained information on asthma patients involved in non-leukotriene modifier clinical drug trials, the period prevalence of CSS was estimated to be 64.4 per million patient-years of observation[12]. The generalizability of these findings are limited, however, due to the selected study populations and methods used to ascertain cases of CSS. Our aim was to estimate the incidence of CSS among a large population of asthma drug users in both ambulatory and hospital settings.

MATERIALS AND METHODS

Setting. This project was conducted at 3 managed care organizations involved in the HMO Research Network Center for Education and Research in Therapeutics (CERT). The CERT program is a national initiative to increase awareness of the benefits and risks of new, existing, or combined uses of therapeutics through education and research[13]. Computerized information systems of all 3 sites contain records on utilization of the large majority of health care services, including medical diagnoses for both inpatient and outpatient visits, procedures, and pharmacy dispensings as well as enrollment and demographic data. These data are collected as part of routine clinical and fiscal activities. Medical records were available for review in both the inpatient and outpatient setting.

Study population and design. We identified all enrollees 18 years of age or older in the 3 study sites who had ≥ dispensings of any of the following asthma drugs during any consecutive 12-month period beginning January 1, 1995 for Site A and Site B and January 1, 1997 for Site C through June 30, 2000: inhaled corticosteroids (beclomethasone, budesonide, triamcinolone, flunisolide, fluticasone, and dexamethasone), cromolyn-like medications (cromolyn sodium and nedocromil), beta agonists (albuterol, terbutaline, isoproterenol, metaproterenol, levalbuterol, salmeterol, bitolterol, isoetharine, pirbuterol, and epinephrine), theophylline preparations, and leukotriene modifiers (zafirlukast, montelukast, and zileuton). To be included in the cohort, enrollees had to have pharmacy benefits and available inpatient and outpatient data. Using automated databases at each study site, information regarding age, gender, health plan enrollment dates, and outpatient asthma drug dispensings was obtained on all identified patients. All hospital discharge and ambulatory codes for relevant diagnoses and procedures suggestive of CSS were identified beginning at the earliest readily accessible date for retrieving these data. Billing information was accessible beginning in 1995 for Site A and Site B and 1997 for Site C.

Case identification. Because CSS is believed to occur principally in individuals with relatively severe asthma, we limited our study to patients with presumed asthma as defined by receipt of 3 or more dispensings of asthma drugs within a 12-month period. Preliminary studies found a low prevalence of an asthma diagnosis among those receiving 2 or more dispensings of an asthma drug in a 12-month period, therefore to increase specificity we limited the population to persons with at least 3 asthma drug dispensings. We identified cases of CSS based on our prior work, which assessed the use of algorithms to identify patients with CSS[14]. To briefly summarize our step-wise approach to algorithm development, first a panel of clinicians and epidemiologists with expertise in pulmonary medicine, rheumatology, and automated health care databases assembled a list of diagnoses and procedures in order to identify potential cases. Then the utilization of the diagnostic codes and procedures of interest among users of asthma drugs at the 3 health maintenance organizations were examined. Based on the utilization results and a prior study that identified patients with CSS using a database[12], 12 combinations of diagnostic and procedural codes (termed "algorithms") were developed to identify potential cases of CSS. The algorithms that were successful in identifying patients with CSS were as follows: (1) codes for both vasculitis and mononeuritis multiplex; (2) codes for both vasculitis and neurologic symptoms; (3) codes for both eosinophilia and vasculitis; (4) 2 or more codes for vasculitis; and (5) codes for both pulmonary eosinophilia and asthma[14]. Therefore, all patients at the participating sites identified by the above algorithms were selected for medical record review.

Medical record review. Trained medical record reviewers at each site abstracted full-text inpatient and outpatient medical records using a structured data collection instrument developed through our previous work and that of others[12,14]. It included data elements corresponding to the American College of Rheumatology (ACR) criteria for the classification of CSS and related conditions that may suggest a diagnosis of CSS[15]. Relevant imaging and neurodiagnostic studies were also abstracted. Pathology reports based on biopsies of lung, pleura, nerve, muscle, and kidney were photocopied. Personal identifiers were eliminated from those copies before they were sent to the investigators. In addition, laboratory test results for antinuclear antibodies, antineutrophil cytoplasmic antibodies, immunoglobulin E levels, erythrocyte sedimentation rates, and rheumatoid factor were recorded, if available. The date of the CSS diagnosis was assigned based on data from the medical record in the following priority: the date recorded by clinicians involved in the patient's care, or if CSS was not recognized by the treating physician, the date when the patient first presented with hypereosinophilia and systemic multi-organ symptoms of the syndrome.

All abstraction forms were reviewed by a rheumatologist (LRH). Subjects identified as having ≥ 2 criteria for CSS based on ACR criteria were sent for second level review by clinical experts, except for the situation of combined asthma and sinusitis in which a third criterion was required before additional review was performed (Table 1). Two clinician-researchers with expertise in CSS (PFW, MEW) each independently reviewed potential cases and categorized them as unlikely, possible, or probable/definite based on their clinical assessment. In addition, the number of criteria present for 2 CSS classification schemes (ACR and Lanham criteria) were also recorded. ACR criteria require the presence of at least 4 of 6 possible criteria in a patient with known vasculitis in order to be classified as having CSS (Table 1). Lanham criteria require that patients have all 3 criteria: asthma, peak peripheral blood eosinophil counts in excess of 1.5×10^9/l, and systemic vasculitis involving 2 or more extra-pulmonary organs.

Discrepancies between expert reviewers' assessments were discussed and resolved by consensus. All reviewers (LRH, PFW, MEW) were blinded to pharmacy records regarding asthma drug dispensings. However, information on asthma drug use may have been documented in the full text medical records, and occasionally these records were copied by the abstractors and attached to the abstraction forms.

Statistical analysis. We calculated incidence rates of CSS overall and according to patient gender, age, and time period (annually for 1995, 1996, 1997, 1998, and 1999, and for the first 6 months of 2000) using the number of new cases (those rated by the experts as having probable/definite CSS) observed as the numerator and the observed person-time as the denominator. Under the assumption that the asthma drug dispensings were a proxy for an asthma diagnosis, person-time began at the date of the first

Table 1. The 1990 ACR criteria for the classification of CSS[15]. For classification purposes, a patient with known vasculitis is said to have CSS if at least 4 of these 6 criteria are present. The presence of any 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%.

Criterion	Definition
Asthma	History of wheezing or diffuse high-pitched rales on expiration
Eosinophilia	Eosinophilia > 10% of white blood cell differential count
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to vasculitis
Pulmonary infiltrates	Migratory or transitory pulmonary infiltrates on radiographs
Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses
Extravascular eosinophils	Biopsy including artery, arteriole, or venule showing accumulations of eosinophils in extravascular areas.

asthma drug dispensing and ended when patients disenrolled from the corresponding health plan, developed CSS, or the study period ended. Rates were reported per million person-years and 95% confidence intervals (CI) were estimated assuming a Poisson distribution.

Institutional review boards at collaborating institutions approved the study. Given the nature of the study, informed consent was waived.

RESULTS

There were 184,667 individuals with 3 or more dispensings of an asthma drug in a consecutive 12-month period contributing 606,184 person-years of exposure. During the study years, these individuals comprised approximately 5.5 to 6% of the total annual adult membership population of the 3 health plans. This prevalence is similar to the prevalence of self-reported asthma among adults in the United States, which is 7.2%[16]. From this population of 184,667 individuals, 444 subjects were selected for chart review based on the algorithms previously shown to successfully identify likely cases of CSS[14]. Of the 444 subjects, 270 had inpatient records, and 404 had outpatient records, associated with diagnosis and procedure codes suggestive of CSS (52% of subjects had both of these). Medical record information was available for all subjects.

Forty subjects met criteria for review by 2 clinical experts (PFW, MEW). Of these 40 subjects, 22 were classified by the expert reviewers as having probable/definite CSS. One patient was removed from the analyses as she was not a new case but rather had been diagnosed with CSS several years prior to the study period; the remaining 21 subjects were incident cases. The mean age of probable/definite CSS patients at the time of diagnosis was 55. Fifteen of the 21 cases were female. A possible or probable diagnosis of CSS was documented in the medical record by the clinicians caring for 16 (76%) of the cases. The remaining 5 patients were diagnosed with either eosinophilic pneumonia or a systemic vasculitis other than CSS. Based on the initial independent classifications of the expert reviewers, 20 of the 21 cases were considered to meet ACR criteria for the diagnosis of CSS. Using the Lanham criteria, only 3 of the cases were agreed upon by both experts to have met all 3 of the required criteria.

The overall incidence of CSS was 34.6 per million person-years (95% CI 21.4–53.0), with no statistically significant difference in the estimates for women and men (Table 2). Overall, asthma drug users aged 50 to 69 years tended to have a higher incidence of CSS than those in the other age groups (Table 2); however, this trend disappeared when examining the results by gender (Table 3). There was a clustering of cases diagnosed in 1997 and 1998 resulting in higher incidence rates for those 2 years and occurring in both genders, although it was not statistically significant (Table 4). While leukotriene modifiers were introduced beginning in 1997, only 2 cases were exposed to these agents, suggesting that their use was not related to the increased incidence of CSS in 1997 and 1998.

DISCUSSION

This study is the first to identify cases of CSS from a large, diverse population of asthma drug users based on ambulatory diagnosis and hospital discharge diagnosis data and provides age- and gender-specific estimates on the incidence of CSS. Over the study period, there was a trend toward an increase in the incidence in 1997 and 1998; however, we cannot be certain whether this occurred by chance or is possibly related to other factors. While the increased incidence of CSS in 1997 and 1998 appeared to be unrelated to exposure to leukotriene modifiers in our population, published reports of CSS developing during treatment with leukotriene modifiers may have increased awareness of the condition resulting in more patients being diagnosed with CSS.

Our estimated incidence of CSS in asthma drug users is somewhat lower than those reported by others[11,12]. Among users of leuktriene modifiers, the incidence of CSS has been estimated to be 60 per million person-years[11]. Wechsler has proposed that use of these novel corticosteroid-sparing agents suppresses asthma symptoms but may allow the unmasking or progression of a systemic eosinophilic syndrome that otherwise would have been masked by systemic corticosteroids[11]. Other researchers have found that patients with asthma receiving leukotriene modifiers generally have more severe asthma[17]. Because severe asthma may be a pre-

Table 2. Number and incidence (per million person-years) of CSS in asthma drug users by gender, age, and year.

Characteristic	No. of Cases	Person-years	Rate (95% CI)
Gender			
Male	6	227658	26.4 (9.7–57.4)
Female	15	378527	39.6 (22.2–65.4)
Age			
18–29	1	76276	13.1 (0.3–73.0)
30–39	4	103467	38.7 (10.5–99.0)
40–49	3	130559	23.0 (4.7–67.2)
50–59	6	107765	55.7 (20.4–121.2)
60–69	5	97791	51.1 (16.6–119.3)
70–79	2	70981	28.2 (3.4–101.7)
80+	0	19347	0
Year			
1995	0	54055	0
1996	2	89665	22.3 (2.7–80.5)
1997	6	115330	52.0 (19.1–113.2)
1998	10	132757	75.3 (36.2–138.5)
1999	2	142927	14.0 (1.7–50.5)
2000*	1	71458	14.0 (0.4–78.0)

* These results are based on only the first 6 months of 2000.

Table 3. Incidence of CSS per million person-years in asthma drug users by age and gender.

	Age Group															
	18–29		30–39		40–49		50–59		60–69		70–79		80+		Total	
	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)
Women	1	21.0 (0.5–116.9)	2	3.0 (3.6–108.3)	3	34.3 (7.1–100.1)	3	43.2 (8.9–126.3)	4	70.1 (19.1–179.5)	2	51.0 (6.2–184.3)	0	0.00	15	39.6 (22.2–65.4)
Men	0	0.0	2	54.3 (6.6–196.1)	0	0.0	3	78.2 (16.1–288.7)	1	24.5 (0.6–136.7)	0	0.0	0	0.0	6	26.4 (9.7–57.4)

Table 4. Incidence of CSS per million person-years in asthma drug users by gender and year of diagnosis.

	1995		1996		1997		1998		1999		2000	
	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)	No.	Rate (95% CI)
Women	0	0.0	1	17.9 (0.5–99.8)	5	89.6 (29.0–161.9)	7	97.1 (39.0–173.4)	2	22.3 (2.7–80.6)	0	0.00
Men	0	0.0	1	29.6 (0.7–164.6)	1	29.6 (0.6–128.8)	3	69.4 (14.3–202.9)	0	0.00	1	37.5 (0.9–209.1)

cursor to the development of CSS, this may in part explain the higher incidence of CSS in this population. In most of the case reports of CSS developing in patients receiving leukotriene modifiers, they were also receiving systemic corticosteroids, again suggesting these individuals had more severe asthma than the general asthma population and thus may be at higher risk for CSS than our study population. Martin and colleagues examined the period prevalence of CSS among patients with asthma enrolled in nonleukotriene modifier clinical drug trials in the United Kingdom and estimated a rate of 64.4 per million person-years among those receiving asthma drugs[12]. Since the estimate was based on the identification of 3 prevalent cases, it limits any comparisons between their results and ours.

Our methodology was similar to Loughlin and colleagues who calculated the incidence of CSS among patients with asthma enrolled in a national health plan based on hospital discharge diagnoses[18]. However, in contrast to our study, they did not access ambulatory medical records or ambulatory pharmacy dispensings. The number of patients identified with CSS based on hospitalization records ranged from 0 using the Lanham criteria to 3 using an adaptation of the ACR definition. The resulting incidence rates ranged from 0 to 67 per million person-years depending on the definition

used. Of note, none of the 3 patients had a diagnosis of CSS recorded in their medical records.

Our study has several strengths. Since it was a population-based evaluation among a large sample of insured adults, it reduced the problems of referral and selection bias as well as uncertainty of denominator populations. This report is also the first to provide age-specific incidence rates and assess recent temporal trends. In addition, previous estimates have relied on many fewer cases of CSS[2,12,19].

There were also a few limitations to our study. We relied on the opinion of experts in identifying cases of CSS rather than strictly using classification criteria, which influenced the incidence calculations, although only one case did not fulfill the ACR criteria for CSS. This method was chosen as the ACR criteria were developed based on studies of patients with well-defined types of vasculitis and were not designed to diagnose patients, particularly in the setting of a retrospective medical record chart review. Previous authors have shown that the ACR classification criteria function poorly when used as diagnostic tools in identifying individual patients with specific forms of vasculitis[4,20,21]. Our incidence rates were influenced by the demographic characteristics of our study population, which consisted of insured persons enrolled in 3 health plans in different regions of the United States. Previous work has shown that the incidence of vasculitis varies depending on geographic region and is influenced by both genetic and environmental factors[22]. Also, because this was a retrospective study, there was limited information available so the reported incidence rates most likely represent a minimum estimate, as patients with less severe manifestations of CSS may not have been identified using diagnosis and procedure codes. Additionally, medical record documentation for some identified individuals was not sufficiently extensive to confirm the diagnosis.

In summary, the incidence of CSS from a population of asthma drug users is greater than that seen in the general population but somewhat less than reported in other populations of asthma drug users; this is likely due to differences in the characteristics of the cohorts studied and methods used to define cases. Our study provides important information regarding the risk of developing CSS among a large population of asthma drug users and highlights the need for greater understanding of the predictors of CSS among patients with asthma.

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