Clinical outcomes and inflammatory biomarkers in current smokers and exsmokers with severe asthma

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Background: Clinical outcomes are worse in current smokers and exsmokers with mild-to-moderate asthma compared with never smokers, but little is known about the influence of smoking status in patients with severe asthma.
Objectives: We sought to examine the association of current or previous cigarette smoking with clinical and inflammatory variables in patients with severe asthma.
Methods: We compared patients' demographics, disease characteristics, and biomarkers of inflammation in current smokers (n = 69 [9%]), exsmokers (n = 210 [28%]), and never smokers (n = 461 [62%]) with severe asthma (n = 760) recruited to the British Thoracic Society Severe Asthma Registry.
Results: Current smokers had poorer asthma control, more unscheduled health care visits, more rescue courses of oral steroids, and higher anxiety and depression scale scores than exsmokers or never smokers. Current smokers had a reduced proportion of sputum eosinophils compared with never smokers (1% and 4%, respectively) and lower fraction of expired nitric oxide (50 mL/s; 14 ppb and 35 ppb, respectively). Exsmokers compared with never smokers had an increased proportion of sputum neutrophils (59% and 43%, respectively) but a similar proportion of sputum eosinophils (3%) and fraction of expired nitric oxide (50 mL/s; 35 ppb). Both current smokers and exsmokers had reduced serum specific IgE levels to several common environmental allergens.
Conclusion: Current smokers with severe asthma exhibit worse clinical and health care outcomes compared with exsmokers and never smokers with severe asthma. Their inflammatory profiles in sputum and blood differ. (J Allergy Clin Immunol 2013;131:1008-16.)

Key words: *Severe asthma, cigarette smoking, exsmokers, asthma control, exacerbations, health care use, airway inflammation, inflammatory biomarker*

Worldwide prevalence of active smoking in adults with asthma ranges from 20% to 35%, which is similar to the prevalence in the general population.[1-3] Smokers with mild-to-moderate asthma have poor levels of symptom control, increased rates of admission to the hospital with acute asthma, and attenuated responses to corticosteroids compared with nonsmokers with asthma.[1,4-6] Noneosinophilic airway inflammation, sometimes associated with neutrophilia, is commonly found in smokers with mild-to-moderate asthma.[1] A further 20% to 30% of adults with asthma are exsmokers,[2,7] and there are data to suggest that clinical outcomes[8] and corticosteroid sensitivity[5] in these patients might lie between those of current smokers and never smokers with asthma.

Severe asthma occurs in 5% to 10% of the asthmatic population. The prevalence of current smokers and exsmokers in this patient group is not certain because current smokers, particularly those with a heavy smoking history, are often excluded from studies of severe asthma. For example, in the US Severe Asthma Research Program[9] and the European Network for Understanding Mechanisms of Severe Asthma[10] cohorts, smokers with 5 or more pack years of tobacco use were excluded. The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR)[11] and British Thoracic Society (BTS) Severe Asthma Registry[12] cohorts, which did not exclude heavier cigarette smokers, report figures of 6% and 4% for current smokers,

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Abbreviations used
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
BTS: British Thoracic Society
CT: Computed tomography
EuroQoL: European Quality of Life
$F_{ENO_{50}}$: Fraction of expired nitric oxide (50 mL/s)
FVC: Forced vital capacity
HAD: Hospital Anxiety and Depression
K_{CO}: Transfer coefficient
RV: Residual volume

respectively, suggesting that active smoking is lower in patients with severe asthma than in the general population or when all patients with asthma are surveyed.[1-3] Interestingly, in these cohorts exsmokers with asthma account for approximately one third of patients with severe or difficult-to-treat asthma.[11,12]

Patients with severe asthma, predominately never smokers, characteristically have persistent symptoms, abnormal lung function, and increased health care use compared with those with nonsevere asthma,[9] and the group with severe asthma have eosinophilic, neutrophilic, mixed granulocytic, or paucigranulocytic types of airway inflammation.[13,14] The clinical outcomes, mechanisms of disease, and response to treatment can differ in current smokers and exsmokers with severe asthma compared with those seen in never smokers with severe asthma. If so, this difference can have important implications for the clinical management of this group of patients. To date, however, there is little information on clinical and physiologic outcomes and immunologic biomarkers of current smokers and exsmokers with severe asthma compared with those seen in never smokers with severe asthma.

We tested the hypothesis that clinical outcomes are worse, that inflammatory biomarkers differ, or both in current smokers and/or exsmokers with severe asthma compared with those seen in never smokers with severe asthma. We analyzed the BTS Severe Asthma Registry population by comparing patients' demographics, disease characteristics, inflammatory biomarkers, and health care use in current smokers and exsmokers with severe asthma compared with those seen in never smokers with severe asthma.

METHODS

Study population

The study population were patients with severe refractory asthma recruited to the BTS Severe Asthma Registry. The BTS Registry includes 7 United Kingdom centers operating established, dedicated multidisciplinary assessment protocols to ensure identification of patients with well-characterized refractory asthma. The registry is hosted online by Dendrite Clinical Systems Ltd (Henley-on-Thames, United Kingdom) and admits password-protected anonymized data. All subjects provide fully informed written consent for their data to be held in the registry. Ethics approval for research analysis of the data has been provided by the Northern Ireland Research Ethics Committee (United Kingdom).

Assessments

Patients at all centers undergo a multidisciplinary systematic assessment, which includes a medical history and examination and use of asthma-specific questionnaires (Asthma Control Questionnaire [ACQ] scores[15]; Asthma Quality of Life Questionnaire [AQLQ] scores [total and individual domains][16]; generic questionnaires, such as European Quality of Life [EuroQoL] health scale and questions scores; and Hospital Anxiety and Depression [HAD] scores). In addition, patients undergo lung function tests (prebronchodilator and postbronchodilator spirometric results, such as FEV_1 and forced vital capacity [FVC]; static lung volumes, such as residual volume [RV] and total lung capacity; and the transfer coefficient [K_{CO}]), measurement of induced sputum eosinophil and neutrophil proportions, measurement of fraction of expired nitric oxide (50 mL/s [$F_{ENO_{50}}$] in parts per billion), allergy assessment (skin prick tests, serum IgE antibody assays, or both), serum eosinophil counts, measurement of total IgE concentrations, measurement of plasma cortisol and prednisolone concentrations, qualitative assessment of lung computed tomographic (CT) scans, and dual-energy x-ray absorptiometry scans. The tests were performed with different equipment across the sites because these data were collected from hospital outpatient clinics and not in the setting of a research trial. Atopy was defined as any positive immediate, 15-minute, skin prick test wheal response of 3 mm larger than that elicited by the negative control or an *in vitro* IgE antibody serologic test (ImmunoCAP or RAST test or equivalent [>0.35 kU] to common inhalant allergens that typically include house dust mite, grass pollen, and cat dander allergens).

Subjects entered into the registry fulfill the American Thoracic Society definition of severe refractory asthma (see the Methods section in this article's Online Repository at www.jacionline.org).[17] They were divided into 3 groups: never smokers, exsmokers, and current smokers. The exsmokers were further subdivided by pack years smoked: less than 10 pack years and 10 or more pack years. An exsmoker was defined as someone who had stopped smoking, and the years since they stopped smoking was recorded.

Analysis

Data were logged and analyzed with statistical software (Minitab Ltd, Coventry, United Kingdom). After inspection, continuous variables were summarized as means (SDs) or medians (interquartile ranges) depending on Gaussian or skewed distribution, respectively. The comparison between different smoking categories was done with 1-way ANOVA and Kruskal-Wallis tests, as well as with appropriate *post hoc* Student *t* tests and Mann-Whitney *U* tests. Categorical variables were summarized by their observed frequencies and percentages within the participant subsets and were compared by using χ^2 or Fisher exact probability tests, including the Freeman-Halton extension for 3×2 contingency tables, as appropriate. The linear relationship between 2 normally distributed continuous variables was measured by using Pearson product moment correlation coefficient; skewed data were analyzed after log or square-root transformation, as appropriate. All analyses were considered descriptive or exploratory, and therefore a P value of less than 5% was considered significant.

RESULTS

Of 1019 patients registered in the BTS Difficult Asthma database, 760 (75%) fulfilled the American Thoracic Society criteria for severe asthma.[17] Data on smoking status were available for 740 (97%) of this group, of whom 62% were never smokers, 28% were exsmokers, and 9% were current smokers.

Patients' demographic data, medical and occupational history, and history of allergen exposure

For more information on patients' demographic data, medical and occupation history, and history of allergen exposure, see Table I.

Current smokers with severe asthma. Current smokers compared with never smokers with severe asthma had a slight predominance of white race (97% vs 88%), an older age at diagnosis of asthma (20 vs 12 years), and a less frequent history of nasal polyps (6% vs 15%) and were less likely to have full-time employment (20% vs 43%). Current smokers compared with