

EDITORIAL

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Exacerbation-prone asthma—intrinsic to severe disease or a unique phenotype?

This editorial discusses the findings of the paper in this issue by M. Kupczyk et al. [10] pp. 212–221.

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Research performed over the past two decades has helped define the inflammatory nature of bronchial asthma and highlight the importance of anti-inflammatory therapy [1]. Despite the advances in management and widespread use of inhaled corticosteroids, acute exacerbations remain a relatively frequent event for many asthmatics. These events may impact greatly on individual patients, with significant reductions in quality of life [2], long-term declines in lung function [3] and rarely death [4]. Asthma exacerbations also give rise to important social costs; hospitalizations constitute one-third of the \$14.7 billion in annual healthcare costs attributable to asthma in the United States [5] and loss of worker productivity due to exacerbations accounts for over half of the €17.7 billion spent annually on asthma in the European Union [5]. Because of these negative consequences, prevention of exacerbations is recommended as a key goal of asthma management [1].

Exacerbations of asthma, including those that require emergency department care or hospitalization, occur variably in patients across all levels of severity. In patients with mild-to-moderate asthma, a recent meta-analysis of data derived from registered clinical trials determined that the rate of exacerbations requiring systemic corticosteroids was 0.2 per patient per year, or 1 event for every five patients [6]. In a separate analysis of clinical trial data in patients with severe asthma, the exacerbation rate was 1.5 per patient per year, suggesting that the frequency of exacerbations is related to the underlying severity level of the disease [7]. While this approach to exacerbation data is important in looking

at large populations and the potential effects of interventions upon an entire group, it does not address the issue of how attacks may be distributed in individual patients.

The Severe Asthma Research Program reported findings from 438 patients with asthma across a broad range of severity levels [8]. A questionnaire regarding corticosteroid-requiring asthma exacerbations demonstrated that patients with severe disease were far more likely to have ≥ 3 exacerbations in the prior year (54%) compared with patients suffering from mild and moderate disease (5% and 13%, respectively). These investigators later reported upon the results of a hierarchical cluster analysis and demonstrated similar findings; the three phenotypes with the most severe asthma required multiple courses of oral corticosteroids (≥ 3 courses in the past year) between twofold and fourfold more often than the two milder phenotypes [9]. These two studies confirm the relationship between asthma severity and severe exacerbations but also reveal that a certain proportion of asthmatics with milder phenotypes may be exacerbation prone. These data create the possibility of a hypothesis that patients with frequent exacerbations may represent a separate phenotype of disease with potentially unique pathogenetic mechanisms.

The study by Kupczyk et al. [10] published in this month's issue of the journal seeks to address this question in an observational study of 169 patients with both severe as well as mild-to-moderate disease [11]. Key features of their study design include the prospective collection and validation of acute asthma events as well as assiduous efforts to maintain adherence with asthma controller therapy. Similar to what has been shown in prior studies, frequent exacerbations (defined as two or more exacerbations during the year of observation) were much more prevalent in severe (30%) compared with mild-to-moderate patients (2.5%). In addition, Kupczyk's study found that patients with severe asthma

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accounted for 28 of the 30 (93%) patients with frequent exacerbations. A subgroup analysis of patients with severe asthma revealed that individuals with frequent exacerbations had a significantly higher percentage of eosinophils in their sputum and higher Asthma Control Questionnaire scores than patients who did not report frequent exacerbations. Taken together, these two findings suggest the possibility that frequent exacerbations are near-universally relegated to patients with severe disease who have more intense eosinophilic inflammation and less clinical control.

As exacerbations are relatively infrequent events and a number of factors may influence their occurrence, the current study raises an important question—over what time period must exacerbations be followed to establish that an individual patient is exacerbation-prone? In research designed to establish whether there is a frequent exacerbation phenotype in patients with chronic obstructive pulmonary disease (COPD), subjects were prospectively observed for 3 years [11]. During that period, the vast majority of patients with frequent episodes of exacerbation during the first year of the study continued to have frequent exacerbations during the

second and third years, demonstrating that this aspect of their disease was relatively stable over time.

Ascertainment of the stability of exacerbation frequency in asthma is important, as patients identified as future exacerbators will be potential candidates for more in-depth initial clinical evaluations and closer longitudinal follow-up, including efforts to optimize adherence to inhaled anti-inflammatory therapy. Strict attention to currently available biomarkers, particularly sputum eosinophils, will be of paramount importance in determining the amount of inhaled corticosteroids required to maintain disease control in the individual patient [12]. When these efforts fail, as they will in certain patients, new medications, including cytokine antagonists directed towards interleukins-4/13 [13] and interleukins-5 [14], as well as others, may provide clinical benefit to asthmatics at highest risk.

Conflict of interest: Dr. Corren is a consultant for and has conducted clinical trials with Sanofi and Genentech, both of whom are developing anti-IL-4/13 or anti-IL-13 antibodies, and conducted trials with Teva, who is developing an anti-IL-5 antibody.

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