CHEST

Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD

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BACKGROUND: Patients with moderate exacerbations of COPD and the eosinophilic phenotype have better outcomes with prednisolone. Whether this outcome is similar in patients hospitalized with a severe exacerbation of COPD is unclear. We investigated the rate of recovery of eosinophilic and noneosinophilic exacerbations in patients participating in a multicenter randomized controlled trial assessing health outcomes in hospitalized exacerbations.

METHODS: Patients were recruited at presentation to the hospital with an exacerbation of COPD. They were stratified into groups according to eosinophilic exacerbations if the peripheral blood eosinophil count on admission was ≥ 200 cells/μL and/or ≥ 2% of the total leukocyte count. Admission details, serum C-reactive protein levels, length of stay, and subsequent rehospitalization data were compared between groups.

RESULTS: A total of 243 patients with COPD (117 men) with a mean age of 71 years (range, 45-93 years) were recruited. The inpatient mortality rate was 3% (median time to death, 12 days; range, 9-16 days). The median absolute eosinophil count was 100 cells/μL (range, 10-1,500 cells/μL), and 25% met our criteria for an eosinophilic exacerbation; in this population, the mean length of stay (in days) was shorter than in patients with noneosinophilic exacerbations (5.0 [range, 1-19] vs 6.5 [range, 1-33]; $P = .015$) following treatment with oral corticosteroids and independent of treatment prior to admission. Readmission rates at 12 months were similar between groups.

CONCLUSIONS: The study patients presenting to the hospital with a severe eosinophilic exacerbation of COPD had a shorter length of stay. The exacerbations were usually not associated with elevated C-reactive protein levels, suggesting that better treatment stratification of exacerbations can be used.

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ABBREVIATIONS: CRP = C-reactive protein; CXR = chest radiograph

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Exacerbations of COPD requiring hospitalization are associated with poorer outcomes, including accelerated decline in lung function[1] and a significant risk of mortality.[2] More recently, epidemiologic studies have suggested that the risk of hospitalization increases with the number of previous admissions.[3] Current guidelines for the treatment of an exacerbation advocate therapy with systemic corticosteroids, whereas antibiotic therapy is recommended for patients who are hospitalized with sputum purulence.[4,5] These treatment responses are aimed at reducing treatment failure events and enabling a shortened length of stay. However, corticosteroid therapy is not without harm[6] and is associated with increased adverse events compared with placebo (including significant hyperglycemia in 50%).

It has long been recognized that sputum eosinophilia is a marker for corticosteroid responsiveness in stable COPD with an associated improvement in lung function, symptoms, and exercise capacity.[7,8] The peripheral blood eosinophil count is a respectable surrogate for sputum eosinophilic airway inflammation during an exacerbation of COPD,[9] and the evidence is increasing to suggest that, in moderate exacerbations, there is a subgroup with eosinophilic inflammation defined as a peripheral blood eosinophil count $\geq$ 2% of the total leukocyte count who particularly benefit from systemic corticosteroid therapy.[10,11] However, whether this scenario is the case in patients hospitalized with severe exacerbations of COPD is unclear. We investigated whether clinical outcomes (including length of hospital stay, readmission rate, and mortality) differ according to admission blood eosinophil count in patients admitted to the hospital with severe exacerbations of COPD who participated in a prospective two-center, randomized acute rehabilitation clinical trial in a post hoc analysis.[12] This question is important because morbidity and mortality following a hospital admission are considerable, and the benefits of better risk stratification and treatment targeting may be particularly important.

Materials and Methods

Data were analyzed from patients with COPD participating in a two-center, prospective, randomized clinical trial investigating whether an early rehabilitation intervention enhances recovery during hospital admission for an exacerbation of chronic respiratory disease.[12] Briefly, this study was a randomized clinical trial of a progressive, exercise-based recovery intervention delivered immediately following unscheduled hospital admission, in patients presenting to the hospital with an acute exacerbation of chronic respiratory disease; patients included those with a known physician diagnosis of COPD with a relevant smoking pack-year history $>$ 10. The intervention comprised individualized involuntary and voluntary exercise training techniques modified to suit the environment of acute illness together with an education and self-management program. Clinical data outcomes were collected at admission (baseline); at discharge from the hospital; and at 6 weeks, 3 months, and 12 months. The results of the original trial were negative for its primary outcome, with no differences in hospital readmission in the following 12 months whether randomized to receive the study intervention or standard care. In this subgroup analysis, data were analyzed for exacerbations of inflammatory phenotypes alone and not corrected for intervention arm.

Patients

Adults aged $\geq$ 40 years, presenting to the acute medical ward at the Glenfield Hospital and Kettering Hospital with an acute exacerbation of a chronic lung disease were recruited to the study. The range of respiratory diagnoses included in the intervention study was physician defined and included COPD, chronic asthma, bronchiectasis, or interstitial lung disease. Patients with COPD had to have evidence of a previous corroborative spirometry or imaging and be current or ex-smokers with a pack-year history $\geq$ 10. Patients were excluded from the study if the acute admission was related to a cardiac event, including heart failure, unstable angina, or acute coronary syndrome, and confirmed by opinion of a cardiology specialist; patients were also excluded if significant musculoskeletal, neurologic, or psychiatric comorbidity existed that would preclude the provision of informed consent or ability to perform the intervention rehabilitation program. Patients with a history or evidence suggesting an acute venous thromboembolic event or pneumothorax were also excluded. Patients with $>$ 4 hospitalizations in the previous 12 months for any cause were also excluded from the study. Only patients with a confirmed diagnosis of exacerbation of COPD were studied in this subgroup analysis and analyzed further. All subjects provided informed written consent, and the study was approved by the local research ethics committee (09/H0403/76).

Measurements

Clinical and demographic data was collected at the time of the admission. Results from spirometry conducted when the patient was in a stable state were recorded according to standard guidelines,[13] and venous blood was drawn for measurement of a full blood count and serum C-reactive protein (CRP). Length of stay, mortality, and hospital admissions from any cause in the 12-month follow-up period were captured by using hospital databases and general

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