EDITORIAL

The Role Played by Exacerbations in the Natural History of Chronic Obstructive Pulmonary Disease

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The clinical course of chronic obstructive pulmonary disease (COPD) includes frequent episodes of increased severity of symptoms, commonly referred to as exacerbations. At first, such episodes of clinical instability were considered mere epiphenomena in the natural history of COPD. However, recent evidence indicates that, quite to the contrary, exacerbations have a negative effect on disease progression. This challenge to the historical position has come about because of a shift in how we conceive the natural history of COPD—now seen not simply as chronic airflow limitation but rather as a complex and multidimensional disease in which inflammation plays a significant etiopathogenic role.

By the middle of the 20th century smoking was known to be associated with increased bronchial mucosal secretion. It was also known that smokers with chronic bronchitis had lowered defenses that resulted in colonization and infection of the lower airway. The so-called "British hypothesis" relied on these observations in suggesting that the fact that only some smokers developed COPD was attributable to chronic bronchial hypersecretion and recurrent respiratory infections.[1] In order to test this hypothesis, Fletcher et al[2] conducted a study which demonstrated that the presence of symptoms of chronic hypersecretion in the absence of airway obstruction—now classified as COPD stage 0 in the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] severity classification—was a benign situation that did not necessarily progress to COPD. The same conclusion was drawn, moreover, with regard to recurring respiratory infections. Ever since these results were published, infections—and consequently, exacerbations—have generally been viewed as transient periods of clinical instability that have no repercussions on the progression of COPD. The study by Fletcher et al did not simply challenge the British hypothesis: it also defined a natural history model for COPD that was widely accepted for decades. According to the scheme proposed by these authors, COPD is characterized by an accelerated loss of lung function. As forced expiratory volume in 1 second (FEV_1) decreases, the characteristic symptoms of the disease appear, leading to a deterioration in health-related quality of life, the development of respiratory failure, and ultimately, premature death. Some 3 decades after this study, however, we know that COPD is rather more complicated. It is now understood to be a chronic inflammatory disease, in which a number of components participate, both pulmonary and systemic.[4] The systemic manifestations—most importantly, cardiovascular and nutritional alterations—can affect COPD prognosis independently of FEV_1.[5,6] This undoubtedly poses new conceptual and therapeutic challenges. The etiopathogeny of the disease is mediated by the presence of an anomalous inflammatory response which may persist in ex-smokers.[7] Lung inflammation typically progresses in line with the course of disease[8] and there is also a switch from an innate immune response in the initial stages to an adaptive one in advanced stages.[8] Recent findings also indicate that COPD is characterized by systemic inflammation that progresses over time.[9,10] Given this new conceptual perspective, it is appropriate to review the influence of exacerbations on the natural history of COPD.

Although there is a wide variety of exacerbation mechanisms, almost all episodes are accompanied by an increase in airway inflammatory response. Elevated neutrophil counts have been observed during exacerbations, both in sputum and in alveolar lavage fluid.[11,12] Likewise, increases have also been observed in a number of inflammatory markers, such as interleukins 6 and 8, endothelin 1, leukotriene B4, and neutrophil elastase.[13-15] As exacerbations resolve, the levels of these markers decrease.[15] Nonetheless, there is debate over whether there is a reversion to the pre-exacerbation baseline situation or whether the inflammation persists to a greater or lesser degree. In studies of a cohort of patients with COPD in London (East London Study), it was observed that, during periods of stability, cases with a history of frequent exacerbations had a greater bacterial load,[16] greater airway inflammation,[13] and accelerated decline in FEV_1 (estimated as 8 mL/year and representing a loss of close to 25%).[17,18] It has also recently been observed, in regard to patients with stable COPD, that there is an association between the presence of respiratory syncytial virus in the sputum,

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Manuscript received July 4, 2006. Accepted for publication August 2, 2006.

airway inflammation, a greater bacterial load, and an accelerated fall in FEV_1.[19] These results, pointing as they do to a link between chronic persistent airway infection, local inflammation and progression of the disease, suggest a certain inconsistency with the results of the study by Fletcher et al.[2] That study included smokers with and without airflow limitation, whereas the studies that link infection with deteriorated lung function only evaluated patients with COPD; they consequently observed greater effects with the advance of the disease or the occurrence of repeated exacerbations. It is therefore likely that the influence of exacerbations depends on the stage of the disease. The Copenhagen City Heart Study[20] confirmed that patients at GOLD stage 0 (ie, with chronic cough and sputum production but no airway obstruction) did not necessarily progress to COPD; this was also a conclusion of the study by Fletcher et al.[2] Nonetheless, in more advanced stages of COPD, mucosal hypersecretion is associated with a fall in FEV_1.[21] Furthermore, an increase in the frequency of airway infections coincides with an accelerated decline.[17-19] Curiously, at GOLD stages 3 and 4, higher percentages of B and T lymphocytes in the peripheral airway have been reported, and this may, in fact, reflect an adaptive immune response to a persistent antigen that may be infectious in nature.[8] Likewise, a persistent inflammatory response has been documented for patients with COPD who had given up smoking.[7] A latent infection would imply an increase in the number of activated T lymphocytes—including memory T cells—capable of perpetuating chronic inflammation.[8]

Elevated levels of various markers of systemic inflammation have been detected during exacerbations.[22,23] In a recent study, Hurst et al[23] observed that the degree of systemic inflammation is related to the degree of airway inflammation and the presence of potentially pathogenic organisms in sputum during exacerbations. The temporal profile for these inflammatory changes, however, remains to be established. Nonetheless, an interesting link can be established between exacerbations and a range of systemic manifestations if systemic inflammation persists, just as happens with pulmonary inflammation. In patients with COPD who present high concentrations of C-reactive protein (a systemic inflammation marker), the risk of a cardiovascular event is considerably increased.[24]

Curiously, cardiovascular morbidity also rises in the peri-exacerbation period. It has been demonstrated very recently that, independently of the main confounders, C-reactive protein may even be a predictor of mortality.[25]

A number of studies have pointed to a noticeable increase in mortality after hospitalization.[26-28] Connors et al[26] observed that patients who required admission as a consequence of COPD exacerbations had a hospital mortality rate of 11%; for those who survived hospitalization, the mortality rate at 1 year was 43%. Lower mortality rates have been found in subsequent studies of patients with less serious COPD; for example, mortality rates at 1 year and at 2 years for a Spanish series were 22% and 36%, respectively.[27] These results would indicate that the main determinant of death following hospitalization is the baseline severity of the disease. In other words, the more severe the COPD, the greater the likelihood of hospitalization and the greater the risk of death. Nonetheless, since we have frequently observed patients with severe COPD who do not present exacerbations and who have not demonstrated a high mortality risk, it may be that it is the exacerbations themselves that indicate a poorer prognosis. We recently concluded a study aimed at analyzing the influence of exacerbations treated in hospital (in emergency department and admitted patients) on survival in COPD.[29] The main findings show that requiring hospital care during an exacerbation behaves as an independent predictor of poorer prognosis regardless of the baseline severity of COPD; in other words, mortality increases significantly as the frequency and severity of exacerbations increase. The risk of death doubled for patients with 1 or 2 exacerbations a year in comparison with patients with no exacerbations and quadrupled for patients with 3 or more exacerbations a year. Exacerbation severity was also related to mortality, in that the mortality rate in cases requiring admission to hospital was greater than in cases treated in an emergency department. In our opinion, these results—particularly if confirmed by further studies—offer a new perspective on COPD, namely, that treatments to reduce the severity or frequency of severe exacerbations may also reduce mortality during these episodes.

Further underlining the need to reduce the severity of exacerbations is the fact that noninvasive mechanical ventilation has been shown to reduce in-hospital mortality,[30] although it has to be conceded that long-term results in this respect are inconclusive.[31] As for prevention, the frequency of exacerbations can be reduced to a greater or lesser degree by a number of treatment approaches: inhaled corticosteroids, long-acting bronchodilators, influenza vaccinations, rehabilitation, physical activity, antioxidants, etc. Of these treatments, inhaled corticosteroids have been the most studied, probably because of their anti-inflammatory action. A number of studies have documented a reduction of around 25% in the number of exacerbations with inhaled corticosteroid use; furthermore this reduction is associated with a significant improvement in quality of life.[32] A recent meta-analysis of a database of 5000 patients enrolled in different clinical trials indicated that these drugs could have a beneficial effect on survival despite their limited effect on lung function.[33] Combined use in the same inhaler of a long-acting β_2-agonist and a corticosteroid has been demonstrated to produce better results than monotherapy; the synergistic action of the 2 drugs produces improvements not only in lung function but also in symptoms, quality of life, and exacerbations.[34,35] More specifically, combined treatment has been shown to reduce the number of exacerbations by around 25%—and by up to 40% for exacerbations that require treatment with systemic steroids. This improvement can be assumed to have a beneficial effect on survival.[34,35] Preliminary results have recently been reported for the TORCH study of around 6200 patients with moderate or severe COPD.[36] The main aim of this study was to evaluate the effect of combined treatment (salmeterol plus fluticasone) on mortality. In the group of patients administered this treatment, mortality was reduced by 17.5% (P=.052). The conclusion was that the combined treatment would improve survival rates for

at least a large number of patients with the disease. If this is the case, this would be the first pharmacological treatment capable of modifying the natural history of COPD. The precise mechanisms underlying the improvement in survival rates are still unclear; that said, in view of the arguments above, a possible mechanism may be the reduction in the number of exacerbations. Since other drugs—for example, tiotropium—have likewise been demonstrated to significantly reduce the number of exacerbations, these could also be expected to have a beneficial effect on survival.[37] Regular physical activity has also recently been associated with reduced COPD mortality, perhaps because it significantly reduces the likelihood of hospitalization.[38] It is also necessary to emphasize the importance of eradicating the germ that causes exacerbations or persistent inflammation. Some studies indicate that eradication of the germ reduces inflammation,[39] and this undoubtedly has implications for disease progression. Finally, a potentially good treatment strategy is to combine all these resources, given that—in specific intervention programs for selected patients—this approach has been shown to substantially reduce hospitalization rates.[40,41]

In conclusion, the abandonment of the traditional concept of COPD and an acknowledgment of the complexity and multidimensionality of the disease opens up new, promising prospects. In particular, exacerbations appear to play a much more relevant role than has previously been assumed; should results from observational studies on the progression of COPD and the corresponding mortality be confirmed, then exacerbations should be prioritized as a therapeutic target.

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