

group, although the FEV₁ did not improve after day 3, it did not deteriorate either.

While this study was only a single-blind one, the authors have provided some insight into the duration of steroids for COPD exacerbations. An evidence-based approach to treating COPD exacerbations would suggest that the appropriate duration of therapy is in the range of 5 days to 2 weeks. The 10-day course has been studied best. Since the median length of hospitalization for an exacerbation of COPD is 7 to 9 days,^{5,6} a convenient practice would be to discontinue steroids at the time of discharge from the hospital.

All of the published studies have excluded patients who received systemic steroids within the preceding month. This might be a substantial number of patients with COPD, among whom are likely to be some of the most impaired as well as some of the most unstable. Whether such patients would still benefit from retreatment with steroids remains unknown. We are moving towards a clearer understanding of the dose, duration, and effectiveness of systemic steroids for managing acute exacerbations of COPD. Further studies like that of Sayiner and colleagues will assist with clinical decision making.

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α_1 -Antitrypsin Deficiency Therapy

Pieces of the Puzzle

The article by Marion Wencker et al in this issue of *CHEST* (see page 737) fits another piece within the yet-unfinished jigsaw puzzle of the pathophysiology and treatment of α_1 -antitrypsin (AAT) deficiency. The molecular and cellular mechanisms leading to this deficiency are among the best understood of the genetic conditions leading to an increased risk for organ dysfunction. The single amino-acid substitution seen in the most common form of AAT deficiency leads to an altered conformation of this protein as it is translated in the hepatocyte.¹ This provokes insertion of the reactive loop of one Z mutation AAT molecule into the A-sheet of another Z mutation AAT molecule, resulting in polymerization and accumulation of AAT within the hepatocyte cytoplasm.² This, in turn, leads to the characteristic periodic acid-Schiff–positive, diastase-resistant hepatocyte granules and a low serum level of this important serine proteinase inhibitor. Lowered levels of AAT bathing the lungs leads to the possibility of connective tissue degradation by phagocyte proteinases, normally inhibited by physiologic concentrations of AAT.³ The insights gained from studying AAT deficiency have provided the basis for our growing comprehension of the mechanisms leading to COPD in general.

Despite this understanding of the basic pathophysiologic mechanisms, it has been difficult to design studies testing the treatment of this disorder. While the prevalence of AAT deficiency in US and European communities is relatively high (as many as 100,000 individuals on each continent), only approximately 6% of affected individuals have been identified to date. Thus, large randomized trials become difficult to enroll. IV augmentation therapy using pooled human plasma AAT (Prolastin; Bayer Biologics; Research Triangle Park, NC) was approved in the United States and several European countries approximately 10 years ago. This approval was based on “biochemical efficacy”: the replacement of a deficient serum protein. The presence of a well-accepted therapeutic option makes the implementation of placebo-controlled trials of clinical efficacy problematic.

The article by Wencker et al attempts to evaluate the clinical efficacy of pooled human plasma AAT therapy using a multicenter, retrospective trial design, evaluating the same patients both before and after initiation of therapy. Previous studies from this group and from the United States National Institutes

of Health α_1 -Antitrypsin Deficiency Registry had detected a decrease in the rate of decline of FEV₁ and improved mortality in treated individuals whose lung function was moderately impaired. The current study of 96 patients showed a statistically significant lower rate of decline of FEV₁ in the whole group during augmentation therapy compared with the pretreatment period. The mean difference in rate of decline was 14.9 mL/yr. Interestingly, there was not a significant difference in the pretreatment-posttreatment rate of decline (-3.7 mL/yr) in 25 patients with FEV₁ < 30% predicted. The difference in pretreatment-posttreatment rate of decline was larger (11.6 mL/yr) but not statistically significant in 60 patients with FEV₁ 30 to 65% predicted. The pretreatment-posttreatment rate of decline was greatest (73.6 mL/yr) and statistically significant in 11 patients with FEV₁ > 65% predicted. Seven patients with a rapid decline of FEV₁ during the pretreatment period within the last group had a pretreatment-posttreatment augmentation therapy difference in FEV₁ rate of decline of 203 mL/yr; four slow decliners showed a difference of -26.4 mL/yr.

One study⁴ has suggested that the rapid decline in lung function seen in AAT-deficient individuals does not follow a straight line or smooth curve but, rather, proceeds in a stepwise fashion with each drop associated with a lung infection or other inflammatory process. Using the pooled information of available studies^{1,5,6} leads to a potential profile of the appropriate AAT-deficient patient to treat with augmentation therapy: one with moderately severe obstructive lung disease, or one with well-preserved lung function but early evidence of a rapid decline. The utility of treating AAT-deficient patients with advanced COPD remains unproven; the results of the current study in 25 patients with initial FEV₁ values < 30% predicted suggest that augmentation therapy is not worthwhile. However, this is a retrospective study, and the results may therefore be biased.

As recently as 1 year ago, pooled human plasma AAT was in short supply in the United States, with individuals with newly diagnosed conditions precluded from initiating therapy; those already receiving therapy were forced to reduce their doses to amounts likely to be ineffective. As these patients changed location, physician, or insurance, they would find themselves unable to receive the drug. These problems have been largely eliminated since November 1, 1999, by an important and unique drug distribution method: direct patient allocation (Bayer Direct). Under this system, the drug is distributed

directly to each patient and the allocation follows the patient regardless of changes in insurance or location.

Another clinical problem of growing magnitude, and which bears importantly on developing screening programs for α_1 -antitrypsin deficiency, is the concern regarding potential genetic discrimination in hiring and insurance. While the gene frequency of AAT-deficient alleles is approximately 21 million individuals in the United States, this condition is still considered quite rare by the practicing physician. Just as large-scale detection efforts were being developed, an appreciation of genetic discrimination issues led to a tabling of these efforts. Until legislative and regulatory proscriptions against such discrimination are in place, the efforts to increase detection of this genetic condition will be thwarted. Regardless, it is anticipated that even the current, relatively meager detection efforts will lead to a worldwide shortage of augmentation therapy in the near future.

In the late 1980s, we congratulated ourselves for having "solved" the riddle of AAT deficiency and its treatment in a mere 25 years. Now, in this new millennium, we see that our celebrations may have been a bit premature.

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