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EDITORIAL

Augmentation Therapy in Alpha-1 Antitrypsin Deficiency

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A deficiency of the circulating serum glycoprotein alpha-1 antitrypsin (α 1-AT) is the most common identified genetic cause of chronic obstructive pulmonary disease (COPD) and is also a risk factor for liver disease in children and adults. Prevalence estimates suggest there are about 100,000 severely deficient adults in the US, and a similar number in Europe, yet only about 6% of these individuals have been identified. Diagnosis requires only a simple blood test.

One reason to identify individuals at risk of lung disease due to α 1-AT deficiency is that specific therapy is available. This therapy, referred to as augmentation therapy, is a human plasma fractionation product highly enriched for α 1-AT protein and is available from a number of companies in the US and Europe. Generically, these products are all labeled: alpha1-proteinase inhibitor, human. In the latter half of the 1980s, the US Food and Drug Administration approved the first of these augmentation therapies based on its biochemical efficacy, that is, its ability to raise blood and bronchoalveolar epithelial lining fluid levels of α 1-AT. Traditional efficacy trials were not feasible prior to marketing approval in large part due of the extremely small number of patients with α 1-AT deficiency identified at that time.

Since the introduction of the first augmentation therapy product, several studies have tried to assess the effectiveness of augmentation therapy at slowing the progression of lung destruction in α 1-AT deficiency. While the results of each of these studies has been encouraging, none have provided definitive proof of effectiveness and each clinician and payor seems to have a different interpretation of the conclusions of these studies, leading to differences regarding the correct patient populations to treat or deny treatment. The metaanalysis in this issue by Chapman and his colleagues (1) attempts to provide a synthesis of existing data on the effectiveness of augmentation therapy in patients with lung disease due to α 1-AT deficiency.

Combining the data from four published, high quality studies with data from the Canadian Alpha-1 International Registry, the authors have summarized and quantified the results of therapy trials in α 1-AT deficiency and conclude that augmentation therapy significantly slows the progression of airflow obstruction due to α 1-AT deficiency. Unfortunately, of the five studies included in this analysis, the data from NHLBI Registry study (2) dominates the results by virtue of its size compared with the other studies. As a result, the overall conclusions of this meta-analysis are very similar to those of this one study alone.

While those awaiting a large, well-powered, randomized, blinded, placebo-controlled trial (something that may never happen) may not find this analysis compelling, those of us who treat this disease every day and have observed the benefits of long-term augmentation therapy see this as another confirmation of our appreciation for this class of therapy.

Less satisfying are the questions left unanswered. When should augmentation therapy be started? What is the best dosage regimen and what is the optimal dose? Will augmentation therapy be effective administered by another route, such as inhalation?

As discussed in the current article, the magnitude of benefit from augmentation therapy is greatest in those with moderate obstruction as judged by FEV1 percent of predicted normal. Some have misinterpreted this result, seen in virtually all of the cited studies, as proof that augmentation therapy is ineffective in those with mild or severe disease. It is important to point out that lack of proof of effectiveness is not the same as proof of lack of effectiveness. There are reasonable explanations for this lack of significant effect in the mild and severe groups. First, the number of subjects in the moderate group was much larger than the number in the groups to either side on this severity scale, thus increasing the power to detect a benefit in the larger moderate severity group.

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Of potentially greater impact is the fact that the mildly obstructed group was dominated by individuals whose lung function hardly changed at all from beginning to end of the observation period. The Wencker study (3) suggests that mildly obstructed patients with rapidly declining lung function actually benefit greatly from augmentation therapy. In the severely obstructed group, the lack of detectable benefit also has a reasonable explanation. Since it is well documented that individuals with severe COPD having a slowing in their rate of decline of lung function, the power to detect a slowing of this already reduced rate of decline becomes vanishingly low.

The results of such studies have led clinicians and insurers to deny therapy to individuals with mild emphysema due to α 1-AT deficiency. A younger deficient individual with documented mild emphysema or an older individual with documented declining lung function but only mild obstruction should be considered for augmentation therapy (provided risk factors such as cigarette smoking have been eliminated). To deny therapy to this group is tantamount to saying, "I'm sorry, I need to wait until your lung destruction is more severe before I prescribe the therapy that has been shown to slow lung destruction in your condition."

Since augmentation therapy is a prophylactic treatment, an important advance would be to identify a method that would detect the subgroup of individuals with α 1-AT deficiency and normal lung function who will go on to develop emphysema in the future, so that augmentation can be started as early as possible. Baseline high resolution CT scanning of the lung may be one approach, since preliminary data from reporting sites indicate that more than half of those with α 1-AT deficiency and normal lung function enrolled in the NIH QUANTUM-1 study have CT evidence of emphysema (4).

Unfortunately, in spite of the compelling evidence presented in the metaanalysis described in this issue, it is unlikely that any regulatory authorities will accept that currently available augmentation therapy is of proven efficacy. Therefore, future studies will be required to be placebo-controlled. The fact that current therapy is now so widely accepted as effective will make it increasingly difficult to enroll subjects in such studies of new therapeutics for α 1-AT deficiency. The double-edged sword strikes again!

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