Bronchodilator Therapy of COPD

A Reanalysis Suggests New Roles and New Concerns

Studies on the therapy of COPD make a frequent appearance in the pages of CHEST and deservedly so. COPD is a common, progressive, and disabling disease. It is also a very heterogeneous disease with multiple therapies. And, as with most diseases that have multiple therapies, none offer a perfect solution (no pun intended). Clearly, as the recent Lung Health Study¹ (LHS) points out, smoking cessation is by far the most important intervention. But what about patients with established disease? The results of the pharmacologic arm of the LHS are viewed as disappointing.² Yes, a bronchodilator effect was seen, but no effect on the progression of disease was seen. In this issue of CHEST (see page 62), results are presented that provide more encouragement for regular use of the bronchodilator ipratropium in advanced COPD. They also suggest that the regular use of β-agonists should be reconsidered in some patients with COPD.

Dr. Rennard and colleagues present a posthoc analysis of studies evaluating 3 months of a β-agonist or ipratropium in patients with moderate and advanced COPD, and they conclude that there are unique and possibly sustained benefits from long-term treatment with ipratropium that are not seen with β-agonists. They utilize data from seven industry sponsored trials performed for the Food and Drug Administration in which ipratropium, a β-agonist, or a combination of ipratropium and albuterol are compared with each other. The authors now present a new analysis looking at the effects of a β-agonist or ipratropium. The seven studies have sufficiently similar study designs to be analyzed together, although they were originally designed to ask different questions than the current analysis. While these facts and the retrospective nature of the analysis mean the results should be viewed with caution, there is much to recommend in the study. First, the data were available and of good quality, and without conducting another major trial, new insights are gained. Second, it is a large and randomized study with a total of 1,445 well-characterized patients with advanced COPD. This makes it one of the largest studies of therapy in this patient population. Although some of these results have appeared twice before in CHEST,³⁴ this study includes a number of previously unpublished studies, and the analysis is fundamentally different from those previously published.

The LHS also evaluated the effect of long-term ipratropium on lung function in a large group of subjects with COPD. Both studies show a similar bronchodilator effect. However, at the end of the LHS, the ipratropium-induced improvement in pulmonary function was lost. In the study by Rennard et al, there appears to be a sustained improvement seen with ipratropium, but not a β-agonist. One difference in the two studies was the duration that the drug was withheld at the end of the study. Does a prolonged (>12 h, <40 h) bronchodilator effect of ipratropium explain the difference? Possibly, and a reevaluation of the pharmacokinetics of inhaled ipratropium in COPD is in order. There are other major differences in the two studies. The most obvious is that Rennard et al evaluated patients with much more severe disease, an average FEV₁ of ≈1.0 L compared to ≈2.6 L in the LHS. Are the study subjects simply at different time points of the same disease? Probably not. The LHS subjects would have to lose FEV₁ at a rate of over 100 mL/yr to develop the disease as severe as in the Rennard et al study. The observed average FEV₁ decline in the LHS was 50 mL/yr. It is therefore likely that Rennard et al looked at a subset of patients with COPD, one characterized by a previously rapid decline in FEV₁. This high-risk subset has been identified several times.⁵⁻⁷ Although there may be a relationship with airway reactivity, the specific mechanisms responsible for the decline are unknown. So is the therapy. Rennard et al may have observed a treatment effect present in such a subset of patients.

The role of β-agonists in this and other subsets of COPD also needs further evaluation. In the Rennard et al report some patients treated with β-agonists showed declines of FEV₁ and bronchodilator responsiveness. The “adverse” effects were most marked in exsmokers and those with a greater FEV₁. It is tempting to speculate that these patients also represent a subset of COPD worthy of further attention and tailored therapy. While the lessons and cautions of regular β-agonist therapy in asthma should not be applied directly to COPD, the present study does suggest β-agonists should be viewed with caution in some patients with COPD, and the benefits and drawbacks of long-term use of β-agonists should be studied specifically in the various COPD subpopulations.

The “β-agonist controversy” is alive and well in asthma, and this report on a large number of subjects should signal a new level of scrutiny for β-agonists in COPD. As with asthma, acute bronchodilation may not be a good marker of the overall effectiveness of a drug. The “β-agonist controversy” in COPD was recently


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reviewed in CHEST, and a call for an analysis such as performed by Rennard et al was made. Now we have one, and the roles of long-term pharmacologic therapy in COPD needs further prospective study in important subsets of COPD, including early disease, as in the LHS patients with rapidly declining pulmonary function, and those at the end of a rapid decline such as the subjects in the study by Rennard et al. For the moment, in patients with advanced COPD, ipratropium appears to be the bronchodilator for regular use with a sustained benefit, little evidence of long-term adverse effects, and possibly some benefits beyond acute bronchodilation.

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Do We Really Know the Value of Surveillance Lung Biopsies?

I read with interest the report by Baz and colleagues in this issue of CHEST (see page 84) on the utility of bronchoscopies after lung transplantation at Duke University. I believe that four important issues need to be emphasized from this study.

First, we cannot be assured that there is an absolute need for surveillance biopsies. The lines are drawn, and opposing opinions today are not closer to resolution than they were 3 to 4 years ago. The issue gets cloudier when you include more recent reports from two of the largest programs in the world: The Papworth Program, leaning away from surveillance, and the University of Pittsburgh, leaning toward it.

Next, at this time, we all need to concern ourselves with costs—and bronchoscopic biopsies are expensive. Surveillance biopsies may potentially cover costs by providing diagnosis of asymptomatic rejection and bronchiolitis obliterans syndrome (BOS). But it is not clear that early diagnosis today prevents BOS.

To that end, the third and fourth issues become concerns—what is the evidence that surveillance biopsies prevent disease or improve survival? Currently, this evidence is lacking, even when one considers the unsuspected asymptomatic diagnoses made by surveillance biopsies. Part of the reason that surveillance approach offers no clear advantage is that the old medical saw, “a high index of suspicion,” leads to similar number of biopsies per patient in the first 1 to 2 years in programs that biopsy for indication rather than surveillance (informal survey). What emerges as the greatest determinant of the frequency of biopsy is the number of clinical events in the first few months after transplantation. Essentially, those who are event-prone continue to have episodes that lead to more bronchoscopies and biopsies.

Baz and colleagues address this very issue indirectly by showing, in a relatively small number of patients, that freedom from rejection or cytomegalovirus in the first 4 months portends an excellent outcome, for the duration of their observation. The controversy, however, continues because it is not clear that patients with early events would not have been diagnosed anyway by development of clinical signs within a short period. The main value from the current paper may be the early identification of a group that can escape further biopsies by remaining event-free shortly after transplantation. Also of note, the results from Bando et al show that patients diagnosed early in the course of chronic rejection had a higher likelihood of achieving remission with aggressive therapy than did those with more advanced disease. This may lead us toward more surveillance.

I, like the authors, urge that a definitive prospective study be conducted. It should be multicenter and designed to address the major issues: (1) the value of surveillance biopsy early after transplantation; (2) the cost benefit of surveillance biopsies; (3) the prevention of BOS; and (4) the improvement in survival.

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REFERENCES

1. Trulock EP, Ettinger NA, Brunt EM, et al. The role of...