

Randomized, Placebo-Controlled Trials in Alpha-1 Antitrypsin Deficiency

Robert A. Sandhaus

Division of Pulmonary, Critical Care Medicine, and Sleep, National Jewish Health, Denver, Colorado

ORCID ID: 0000-0002-7937-2485 (R.A.S.).

Abstract

Alpha-1 antitrypsin deficiency (AATD) is a condition caused by the inheritance of two mutated SERPINA1 gene alleles. Individuals with AATD are at increased risk of injury to the liver and lungs. The pulmonary manifestations include precocious onset of pulmonary emphysema and bronchiectasis. For nearly three decades, treatment has been available to individuals with emphysema caused by AATD, but this therapy—augmentation of plasma and tissue alpha-1 antitrypsin levels by intravenous administration of human plasma-derived protein—was approved by regulatory authorities based on its biochemical efficacy. This therapy appears to slow the progression of emphysema in patients with AATD. The medical, patient, and regulatory communities

have sought assurance that this expensive therapy provides measurable clinical benefit. Documenting such benefit has been difficult because of the slow progression of the underlying lung disease in AATD, the rarity of this genetic condition, and the lack of direct quantitative measurements of emphysema progression. Over the past decade, quantitative computed tomography (CT) densitometry of the lungs has been found to correlate with severity and progression of emphysema. The recent publication of a well-powered, masked, placebo-controlled study using CT densitometry to evaluate the effectiveness of augmentation therapy at slowing the progression of emphysema has provided some assurance of the clinical efficacy of this therapy.

Keywords: alpha-1 antitrypsin deficiency; augmentation therapy

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Correspondence and requests for reprints should be addressed to Robert A. Sandhaus, M.D., Ph.D., Division of Pulmonary, Critical Care Medicine, and Sleep, National Jewish Health, 400 Jackson Street, Denver, CO 80206. E-mail: sandhausr@njc.org

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The appropriate treatment of the deficiency of alpha-1 antitrypsin has been the subject of much discussion among scientists and clinicians around the world. Currently, the only specific therapies for alpha-1 antitrypsin deficiency (AATD) are aimed at slowing the progression of lung destruction by providing supplemental alpha-1 antitrypsin protein to the lungs. Among therapies currently approved by regulatory authorities, the route of administration is intravenous and the alpha-1 antitrypsin protein is purified from the plasma of healthy human donors.

This therapy is widely known as “augmentation therapy” and will be referred to as such here. The biochemical

effectiveness of augmentation therapy at raising blood and bronchoalveolar lavage fluid levels of this protein is essentially undisputed. The clinical effectiveness of this therapy and its appropriate dosing are the subject of debate. Although U.S., European, and other regulatory authorities have approved augmentation therapy for the treatment of lung disease due to AATD, many countries in Europe, the Americas, and the rest of the world have not accepted this therapy due to its perceived lack of documentation of clinical effectiveness.

Because additional data have been generated in recent months, it seems appropriate to review the evidence of effectiveness of this widely used therapy.

Evaluations of Effectiveness

There are a variety of methods available to evaluate clinical efficacy and effectiveness. In general, efficacy in this setting refers to the ability to demonstrate a desired clinical effect in humans by doing a study. Effectiveness is used to describe the observation of a beneficial effect in the population using a given therapy. Efficacy is judged in the controlled environment of a clinical trial, whereas effectiveness tends to describe real-world use of a therapy. The distinction tends to be blurred in the setting of an intravenous therapy that is administered by a nurse or other healthcare professional in a clinical setting.

There are a variety of ways to evaluate the effectiveness of a therapy. Simple tradition and long experience with a therapy may lead to an understanding that a particular therapy is effective. This is the case for many long-standing interventions, from a cool, wet cloth on the forehead to relieve the discomfort of a fever to a variety of herbal and traditional medicines used around the world. Many of these often stand up to the more rigorous evaluations about to be described.

The demonstration that a therapy has the ability to affect a biochemical pathway or a mediator known to be related to disease can provide sufficient confidence that it is considered effective. This is the approach that led to the initial approval of augmentation therapy in a number of countries in the latter years of the 1980s. This has been referred to as a demonstration of biochemical efficacy.

There are a variety of ways that clinical questions can be answered using evaluations of existing patients on a particular therapy. In the evaluation of AATD, variations on case-control study designs have been used in which investigators compare individuals on a given therapy with historic control subjects or with similar individuals who happen not to be receiving that therapy.

The “gold standard” for prospectively evaluating clinical effectiveness of a therapy is a randomized, blinded (or masked), placebo-controlled trial with clearly defined, well-accepted clinical endpoints. These trials are often referred to as RCTs, for randomized controlled trials. One or more RCTs demonstrating the efficacy of a therapy are usually required for the approval of modern drugs and treatments by regulatory authorities like the U.S. Food and Drug Administration or the European Medicines Agency. A well-designed RCT must have clearly defined clinical targets that can be measured (endpoints) and must evaluate sufficient numbers of subjects so that the comparison of these endpoints between the treated group(s) and the control or placebo groups can be evaluated statistically; that is to say, it must be well-powered. Another consideration is whether the magnitude of an observed benefit, although statistically significant, is clinically meaningful.

Clinical Trials in AATD

Thirty years ago, in the early days of augmentation therapy for AATD, the measurements available to evaluate the lung destruction associated with AATD were crude and inexact. More importantly, the number of identified individuals with AATD at that time was quite small—too small, in fact, to perform a well-powered clinical trial. Taking these factors into account, a number of countries approved the use of augmentation therapy based on its biochemical efficacy (1, 2). Many clinicians and payors were not convinced that evidence of biochemical efficacy was sufficient to adopt this therapy and wanted additional documentation of clinical benefit.

Initially, investigators relied on patient registries (3), case-control or historical-control clinical trials (4–6), or comparisons of patients with AATD living in countries where augmentation therapy was widely available versus those in countries where it was not (7). Although a fair number of these trials were performed in the decades after regulatory approvals of augmentation therapy, each study appeared to have flaws in the comparison of the treated versus untreated participants. These included differences in the socioeconomic status of one group versus another, differences in the care received by one group versus another, or other differences that could presumably influence the outcome of the comparison. Among all these studies in AATD, what was most remarkable was the consistency of the clinical benefits measured in those who received augmentation therapy compared with those who did not.

All of these studies evaluated the effect of augmentation therapy on rate of decline of lung function as measured by spirometry. Specifically, the FEV₁ was followed over time to see if the accelerated rate of decline was reduced. Certain subgroups seemed to benefit more than others. For example, in some trials (3, 7), having moderate obstruction at entry in the registry or study yielded more significant benefit. In others (6), having a rapid rate of FEV₁ decline before starting therapy yielded more significant reductions.

But regulatory authorities, payors, patients, and the medical community wanted better documentation that augmentation therapy actually provides

clinically meaningful benefits for those who are prescribed this expensive therapeutic. Companies that manufacture augmentation therapy were charged with designing an RCT approach to address these issues.

In 1999, Dirksen and colleagues (8) reported on a relatively small RCT (total of 56 Dutch and Danish subjects) comparing lung-affected individuals with AATD who were randomly assigned to receive monthly intravenous infusions of augmentation therapy or intravenous placebo. Each subject was followed for at least 3 years. In addition to following spirometry, they used densitometry of computed tomography of the chest (CT densitometry), a relatively novel technique, to quantify the amount of emphysema in each individual during their time in the study. Their 1999 paper described a trend toward less lung destruction in those individuals who were randomized to receive augmentation therapy than in those on placebo. From this study the authors were able to calculate how large a study would be needed to be likely to lead to statistically significant results, if augmentation therapy truly had a beneficial effect on the loss of lung tissue associated with ongoing emphysema.

Ten years later, a second RCT was reported (9). This study of 77 subjects randomized to receive weekly augmentation therapy or placebo for 2 to 2.5 years again evaluated subjects using CT densitometry and again demonstrated trends in favor of augmentation therapy. A metaanalysis that combined the above pair of RCTs demonstrated highly significant benefits in preserving lung tissue as measured by CT densitometry (10).

Finally, in 2015, an RCT powered based on the previous CT densitometry studies was published (the RAPID trial [intravenous augmentation treatment and lung density in severe alpha-1 antitrypsin deficiency: a randomized, double-blind, placebo-controlled trial]). It compared augmentation therapy administered intravenously at 60 mg/kg of body weight each week to placebo infusions in 180 subjects from 13 countries (11). This study revealed statistically significant reduction of the rate of lung density decline over 2 years in the treated group when CT densitometry at total lung capacity was compared. No benefit was demonstrated in FEV₁, symptoms, or exacerbations. In addition, after the 2 years of the randomized trial, all non-U.S. study subjects were offered the opportunity to

receive augmentation therapy for an additional 2 years in an open-label extension with continued monitoring of CT densitometry (the RAPID extension trial). Virtually all eligible subjects agreed to continue for the second 2-year interval. Continued effectiveness was demonstrated in those who were on therapy for all 4 years. Those who were on placebo for the first 2 years, then moved to augmentation therapy for the second 2 years, showed a reduction in the rate of decline of lung density similar to the initial treated group (Figure 1).

Discussion

A single well-powered RCT evaluating intravenous augmentation therapy for the treatment of AATD has now been completed and published. It provides confirmation that lung tissue loss, assessed by CT densitometry, is slowed in those receiving this therapy. CT densitometry of the lung is not a methodology that is widely available, and it is certainly not considered a routine clinical evaluation. CT densitometry appears to be a more sensitive and direct measure of the lung destruction associated with pulmonary emphysema than spirometry or symptom scores (8), which are more reflective of airway disease in chronic obstructive pulmonary disease. Whether CT densitometry measurements

predict more important outcomes, such as mortality and disability, remains to be demonstrated. It is also worth noting that a 2010 publication in the *Cochrane Review* dismissed CT densitometry as a meaningful clinical endpoint in its publication about the status of efficacy trials of augmentation therapy in AATD (12). This review, limited to analyzing the two small RCTs available at the time, concluded that “augmentation therapy with alpha-1 antitrypsin could not be recommended, in view of the lack of evidence of clinical benefit and the cost of treatment” (12).

Although the RAPID trial demonstrated a reduction in the rate of decline of CT lung density when augmentation therapy is given, there are no longitudinal data on the loss of lung density assessed by this technique in a healthy adult population. Thus, none of the studies cited let us evaluate how close the treated group approached a normal rate of lung density decline. Similarly, we have no data that evaluate whether the augmentation therapy dose administered in these trials, or in clinical practice, is the optimal dosing regimen.

Most clinicians evaluating patients with emphysema use spirometry to evaluate the respiratory status of individuals with obstructive lung disease. Specialists may add more complete pulmonary function testing and visual evaluation of a chest CT scan. None of

these more usual clinical tests have been able to detect a clinically beneficial effect of augmentation therapy in the currently completed RCTs. The usual explanation is that a study with these more usual clinical endpoints would require a much larger number of subjects followed for a considerably longer duration. Several of the case-controlled studies that followed patients for longer periods did demonstrate improvements in the rates of decline of lung function and, in the case of the largest of these, survival benefits (3). It should be noted that none of the trials to date have demonstrated any beneficial, or detrimental, effect on the liver disease of AATD, and none was expected, based on the known pathophysiology of liver disease in this condition.

The completion of a single well-powered, randomized, double-blind, placebo-controlled trial of augmentation therapy in AATD will not be convincing to all that this therapy is effective at protecting lung tissue from the destructive processes associated with this genetic condition. Still, it confirms the clinical experience with this therapy over the decades it has been available. An additional goal of documenting clinical benefit for augmentation therapy is that future studies and future therapies can be compared with existing augmentation rather than placebo. Unfortunately, future placebo-controlled trials will likely be difficult to enroll as more and more potential subjects and researchers perceive augmentation therapy as effective.

In general, individuals with severe AATD are provided augmentation therapy when they have evidence of pulmonary emphysema. Universal treatment of those with AATD is not recommended because many individuals with severe AATD never develop clinically significant lung disease. Augmentation therapy appears to slow the destruction of lung tissue but does not reverse damage that has already taken place. Earlier detection of lung injury in AATD may allow augmentation therapy to preserve additional lung tissue. Such early detection requires both improved identification of individuals with AATD and the development of more sensitive measures of lung injury. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

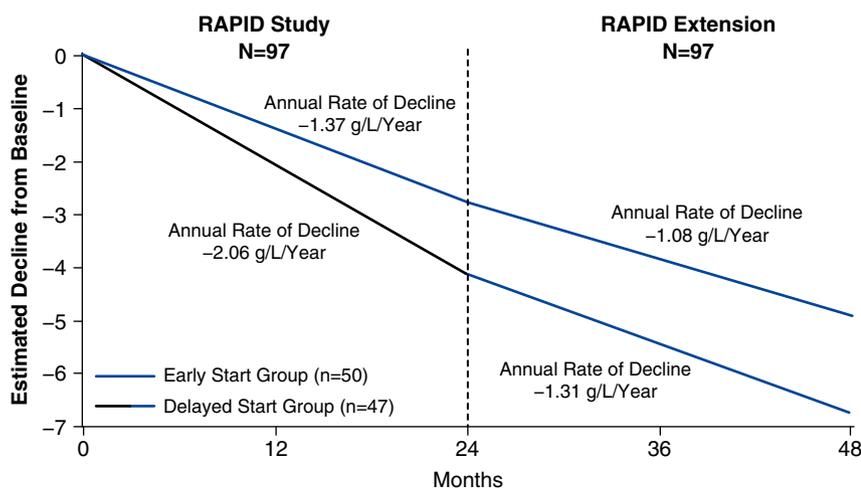


Figure 1. RAPID (intravenous augmentation treatment and lung density in severe alpha-1 antitrypsin deficiency [RAPID]: a randomized, double-blind, placebo-controlled trial) trial and extension results. During the first 24 months subjects were randomized to receive either study drug or placebo; during the second 24 months all received study drug. Only subjects who completed 48 months are included in this analysis. Reprinted by permission from Reference 11.

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