Feasibility of a Clinical Trial of Augmentation Therapy for α_1-Antitrypsin Deficiency

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We examined the feasibility of a randomized clinical trial of intravenous augmentation therapy for individuals with alpha 1-antitrypsin (α1AT) deficiency, basing calculations on newly available data obtained from the NHLBI Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin. Using rate of FEV_1 decline as the primary outcome and adjusting for noncompliance, a study of subjects with Stage II chronic obstructive pulmonary disease (COPD) (initial FEV_1 35 to 49% predicted) with biannual spirometry measures obtained over 4 yr of follow-up would require 147 subjects per treatment arm to detect a difference in FEV_1 decline of 23 ml/yr (i.e., a 28% reduction), the difference observed in the NHLBI Registry (1-sided test, $\alpha = 0.05$, 90% power). To detect a 40% reduction in mortality in a 5-year study of subjects with baseline FEV_1 35 to 49% predicted, recruited over the first 2 yr and then followed an additional 3 yr, 342 subjects per treatment arm would be needed. Though significant impediments to carrying out a clinical trial exist, including the cost of such a trial and the potential difficulties in recruiting patients for a placebo-controlled trial, we recommend a randomized controlled trial as the best method to evaluate the efficacy of intravenous augmentation therapy and of possible future treatments. Schluchter MD, Stoller JK, Barker AF, Buist AS, Crystal RG, Donohue JF, Fallat RJ, Turino GM, Vreim CE, Wu MC, for the Alpha 1-Antitrypsin Deficiency Registry Study Group. Feasibility of a clinical trial of augmentation therapy for α_1-antitrypsin deficiency.

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Alpha 1-antitrypsin (α1AT) deficiency is an hereditary disorder characterized by low serum levels of α1AT, a predisposition to early-onset emphysema, and less commonly, liver disease, including both cirrhosis and hepatoma (1–3). Because the pathogenesis of emphysema in α1AT deficiency involves accelerated lung tissue destruction resulting from unopposed elastolysis, therapeutic efforts to date have focused on augmenting serum and lung levels of α1AT, by promoting endogenous production of α1AT by the liver, or by intravenously infusing purified pooled human plasma α1AT (a treatment known as intravenous augmentation therapy) (4). Although intravenous augmentation therapy has been demonstrated to have "biochemical efficacy" in achieving and maintaining elevated serum and lung α1AT levels (5–7), its clinical efficacy in reducing rate of decline in lung function or improving survival has not been demonstrated. Though a randomized controlled trial was initially considered when the current commercially available pooled human plasma antiprotease (Prolastin, Bayer, Inc., West Haven, CT) was first proposed for Food and Drug Administration (FDA) approval in 1989, it was not undertaken then because the large number of subjects and length of the study dictated by power calculations made the study logistically difficult and prohibitively costly (8, 9). Instead, the National Heart, Lung, and Blood Institute (NHLBI) formed a Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin (10). Recently published results from this Registry (11) suggest that augmentation therapy is associated with an improved survival rate among all subjects, and a reduced rate of FEV_1 decline in patients with FEV_1 35 to 49% predicted, though the authors strongly qualify the results by noting that definitive conclusions will require a randomized clinical trial. Similarly, results from a study comparing German augmenta-

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tion therapy recipients with Danish nonrecipients suggest that those receiving intravenous augmentation therapy have a slower rate of decline of lung function (12). However, the absence of results from a definitive randomized, placebo-controlled clinical trial precludes definitive conclusions regarding the clinical efficacy of intravenous augmentation therapy. Consequently, many investigators and professional societies have continued to recommend a randomized clinical trial of intravenous augmentation therapy (13, 14).

This study reexamines the sample size requirements for a clinical trial, with calculations based on newly available data on rates of FEV_1 decline and mortality, obtained from the NHLBI Registry.

METHODS

The NHLBI Registry

The Registry was initiated in 1988 as a means of collecting information on the natural history of α1AT deficiency with and without augmentation therapy. Details of study design and baseline characteristics have been described previously (10, 15). From March 1989 through October 1992, 1,129 eligible subjects were enrolled and followed at 37 centers. Eligible subjects were ⩾ 18 yr of age and had severe deficiency of α1AT, defined as a serum α1AT level ⩽ 11 μM, confirmed by a Central Laboratory (n = 1,026), or a ZZ genotype confirmed by DNA gene probe analysis (n = 103). Follow-up continued through April 1996 with participants returning for annual or semiannual visits. Spirometry was performed pre- and postbronchodilator using a standard protocol, with ongoing efforts to ensure high-quality, reproducible spirometry results (16).

Sample Size for a Clinical Trial with FEV_1 Slope as Outcome

We assume that measurements of FEV_1 follow a linear random effects model (17), which specifies that each subject's measurements of FEV_1 follow a linear regression over time, with random intercept and slope. Under this model, if n subjects each have FEV_1 (ml) measured at k visit times (years), $t_1, t_2,\ldots,t_k$, the estimated mean FEV_1 slope in ml/year for the group has variance σ^2/n where

$$\sigma^2 = \sigma_b^2 + \sigma_e^2/\Sigma(t_j - \bar{t})^2,$$
$$\bar{t} = \Sigma t_j/k,$$

σ_b is the between-person standard deviation of slopes (ml/year), and σ_e is the within-person standard deviation (ml). In order to be able to detect a difference in mean slopes of Δ (ml/year), with power 1-β using a 1-sided α-level test, the required sample size, n, per group is:

$$n = 2\sigma^2(z_\alpha + z_\beta)^2/\Delta^2,$$

where z_α and z_β are upper α and β percentiles of the standard normal distribution, respectively. In these calculations, we assume that FEV_1 is measured twice yearly.

In practice, the sample size for a clinical trial must usually be adjusted (increased) to account for noncompliance. For example, an actual trial would have some patients originally assigned to therapy who stop taking therapy (drop-outs), and might also have some patients originally assigned to the placebo group who decide to begin taking therapy (drop-ins). Under the standard "intent-to-treat" analysis paradigm, all follow-up data from these patients would be included in the group to which they were originally randomized. The effect of such drop-ins and drop-outs is to reduce the magnitude of the overall treatment effect, Δ, and therefore to increase the required sample size. We therefore inflated the sample sizes by 25% to account for drop-ins and drop-outs. This degree of inflation is needed if one assumes that the drop-in and drop-out rates are approximately 10% each, and the rate of FEV_1 decline of drop-outs and drop-ins is half-way between those receiving and not receiving therapy.

Following previous conventions (11), we examine sample size for clinical trials of the following subgroups, determined by the subjects' initial FEV_1 percent predicted: Stage II chronic obstructive pulmonary disease (COPD) (FEV_1 35 to 49% predicted), Stage I COPD (FEV_1 50 to 79% predicted), Stages I and II combined (FEV_1 35 to 79% predicted), and individuals with FEV_1 30 to 65% predicted (18). Estimates of the variance components, σ_b^2 and σ_e^2, were obtained by fitting a linear random effects model to the FEV_1 changes from baseline as previously described (11), where only the time on augmentation therapy was included as a continuous covariate. The estimate of the difference in FEV_1 rates of decline between recipients and nonrecipients of augmentation therapy, Δ, was obtained in a similar model, which also adjusted for FEV_1 percent predicted, sex, age, current smoking status, and bronchodilator responsiveness (never versus ever). Because these analyses stratify on the subjects' initial (baseline) FEV_1 percent predicted, they differ slightly from results previously reported (11), which stratified on the average FEV_1 percent predicted across all follow-up visits.

Sample Size for a Clinical Trial with Survival as Outcome

Sample size calculations were performed for the log-rank test (19, 20), assuming a study lasting 5 yr, with subjects enrolled uniformly over the first 2 yr. As noted previously, sample sizes were inflated by 25% to account for noncompliance (drop-outs or drop-ins). We examined two subgroups of patients: those with initial FEV_1 35 to 49% predicted (Stage II COPD), and, following calculations similar to those in Idell and Cohen (8), the group with initial FEV_1 25 to 65% predicted. Sample size calculations require specification of the mortality rate in the control group (i.e., the group not receiving augmentation therapy), and the risk ratio (relative reduction in mortality) due to augmentation therapy. For each subgroup, we estimated the mortality rate of those who never received augmentation therapy using an exponential model. We then estimated the risk ratio and percent reduction in mortality comparing those who received versus those who did not receive augmentation therapy using a proportional hazards regression model, adjusting for age, education, and lung transplant status (11).

RESULTS

Sample size calculations using FEV_1 decline as the primary outcome are summarized in Table 1. This table presents estimates of the variance components, estimates of treatment effect, and the sample size necessary to detect treatment effects of this magnitude, for studies where subjects are followed 3, 4, and 5 yr. Note that in a 5-yr study where subjects are recruited evenly over the first 2 yr, the average length of follow-up would be 4 yr. For example, if subjects with initial FEV_1 35 to 49% predicted are followed for 4 yr, a trial would require 147 patients per treatment arm to detect a difference in FEV_1 slopes, Δ (also called the effect size), equal to 23 ml/yr, the difference observed in the NHLBI Registry. Alternatively, 164 subjects per group would be needed if the entry criteria are widened to include those with initial FEV_1 30 to 65% predicted. Because smaller effect sizes were observed in the NHLBI Registry among subjects with initial FEV_1 50 to 79% and 35 to 79% predicted, the estimated sample sizes to detect these differences are larger than those calculated for the subgroups 35 to 49% or 30 to 65% predicted.

Sample size calculations with mortality as the outcome are summarized in Table 2. For the subgroup 35 to 49% predicted, those receiving augmentation therapy had an observed 75% reduction in mortality compared with those not receiving therapy, and a clinical trial would require 83 subjects per group to detect this difference. Larger sample sizes of 208 per group, or 342 per group would be needed to detect a 50% or 40% reduction in mortality, respectively. Sample sizes required for a trial with subjects with initial FEV_1 25 to 65% predicted (Table 2) are only slightly larger than those required for the group 35 to 49% predicted. For example, to detect a 40% reduction in mortality, 380 subjects per group are needed.

TABLE 1

SAMPLE SIZE ESTIMATES FOR A TRIAL WITH FEV_1 DECLINE AS OUTCOME*

FEV_1 % Predicted	FEV_1 Slope in Untreated (*ml/year*) (95% CI)	Effect Size, Δ		Estimates of Variance Components		Required Sample Size per Treatment Arm		
		Δ ml/year (95% CI)	% change	σ_b, ml/year (95% CI)	σ_e, ml (95% CI)	3-yr Follow-up	4-yr Follow-up	5-yr Follow-up
35–49%	−81 (−62, −99)	23 (4, 42)	28%	52 (42, 60)	114 (107, 120)	188	147	128
50–79%	−85 (−65, −106)	14 (−8, 36)	16%	60 (48, 70)	123 (115, 131)	632	507	449
35–79%	−83 (−69, −97)	15 (0, 31)	18%	57 (49, 63)	118 (113, 123)	494	403	355
30–65%	−87 (−73, −100)	21 (8, 35)	24%	50 (44, 56)	113 (108, 117)	213	164	143

* Calculations are for a one-sided test, $\alpha = 0.05$, power = 90%, with FEV_1 measured twice yearly. Sample sizes have been inflated by 25% to adjust for subjects who stop augmentation therapy after assignment to the treatment group ("drop-outs") and subjects who begin augmentation therapy after assignment to placebo ("drop-ins"). If the test is two-sided rather than one-sided, sample sizes should be further increased by 23%.

DISCUSSION

Our results, which are based on prospectively collected data from the NHLBI Registry, may be compared with previous calculations performed using estimates of variability in rate of FEV_1 decline and mortality obtained from retrospectively collected data (8). As an example, for subjects with baseline FEV_1 30 to 65% predicted, Idell and Cohen (8) estimated the between- and within-subject standard deviations of FEV_1 slope to be 114 ml/yr and 155 ml, respectively. These estimates are considerably higher than the estimates obtained from the NHLBI Registry (50 ml/yr and 113 ml, respectively) for the same subgroup. The lower variability observed in the NHLBI Registry can be ascribed at least in part to the prospective data collection, with attention to quality assurance of pulmonary function testing (16). Interestingly, the estimates of the mean rate of FEV_1 decline for this subgroup were similar, with Idell and Cohen (8) reporting a mean decline of 89 ml/yr and the NHLBI Registry reporting a mean decline of 87 ml/yr. Idell and Cohen calculated that a study with 4 yr of follow-up and with FEV_1 measured four times per year would require 197 subjects per group to detect a 40% reduction in mean rate of FEV_1 decline between the groups, which corresponds to a mean difference of 36 ml/yr (1-sided test, alpha = 0.05, power = 90%). However, data from the NHLBI Registry (Table 1) suggest that the actual difference in rates of decline may be smaller (estimated to be 21 ml/yr in Table 1). Using the current estimates of variability, and allowing for noncompliance, we estimate that 164 subjects per group are needed to detect this smaller mean difference of 21 ml/yr, with subjects followed for 4 yr and two measurements of FEV_1 per year. Thus, our current data suggest that the number of subjects per group needed to detect a 23% difference in mean rates of decline (164 per group) is smaller than the number previously estimated to detect a 40% difference (197 per group).

Similar comparisons can be made regarding sample size calculations for a clinical trial with survival as the primary outcome. Based on their sample population of patients with initial FEV_1 23 to 65% predicted, Idell and Cohen (8) estimated required sample sizes of 584, 315, and 192 subjects per treatment arm to detect a 30%, 40%, and 50% reduction in mortality (1-sided test, alpha = 0.05, 90% power). If these sample sizes are inflated by 25% to allow for noncompliance, as we have done in Table 2, they become 730, 394, and 240, which are close to the sample sizes reported in Table 2 (720, 380, and 232 subjects per group, respectively).

Because sample size estimates depend critically on the magnitude of the effect size chosen, it is important to justify this effect size as being clinically significant and not overly optimistic. For determining sample size requirements of a trial using FEV_1 decline as a primary outcome, we used effect sizes observed in the NHLBI Registry. Specifically, a treatment effect of 23 ml/yr, representing a 28% reduction in rate of FEV_1 decline, was chosen for a trial examining the subgroup of patients with FEV_1 35 to 49% predicted. Several lines of evidence support this choice of 23 ml/yr as a clinically meaningful effect size. First, this effect size closely resembles those considered important in other large studies examining treatments for patients with COPD. For example, in the Lung Health Study, the effect size chosen to detect the effect of inhaled ipratropium bromide inhalation and smoking cessation versus usual care was 7.5 ml/yr (21). This estimate was based on an anticipated clinically important treatment effect of 15 to 30 ml/yr with allowance for noncompliance and drop-out. Similarly, in the recently published European Respiratory Society Study on Chronic Obstructive Disease (EUROSCOP) study of long-term inhaled budesonide for mild COPD in smokers, an effect size of 20 ml/yr was considered clinically meaningful (22). As a second line of evidence, the effect size of 23 ml/yr closely resembles that observed in other studies regarding the efficacy

TABLE 2

SAMPLE SIZE ESTIMATES FOR A TRIAL WITH MORTALITY AS OUTCOME*

Baseline FEV_1 % Predicted	% Reduction in Mortality	Required Sample Size per Treatment Arm
35–49%	30%	648
	40%	342
	50%	208
	75%†	83
25–65%	30%	720
	40%	380
	50%†	232

* Calculations are for a one-sided test, $\alpha = 0.05$, power = 90%, assuming a 5-yr study with accrual during the first 2 yr, and 3 yr additional follow-up, and assuming annual mortality rates in the untreated group of 8.7% and 7.8%, respectively, for subjects with baseline FEV_1 35 to 49% and 25 to 65% predicted. Calculated sample sizes were inflated by 25% to allow for drop-outs and drop-ins. If the test is two-sided rather than one-sided, sample sizes should be increased further by 23%.

† The difference observed in the NHLBI Registry (11). Ninety-five percent confidence intervals for percentage of reduction in mortality are (35%, 90%), and (14%, 71%) for subjects with baseline FEV_1 35 to 49% predicted, and 25 to 65% predicted, respectively.

of intravenous augmentation therapy. Specifically, in a large observational study comparing the rate of FEV_1 decline in 198 PI*Z German augmentation therapy recipients versus 97 PI*Z Danish nonrecipients, a difference of 22 ml/yr was deemed both clinically and statistically significant ($p = 0.02$). Alternatively, the use of the 75% mortality reduction observed in the Registry as an effect size for a trial with mortality as an endpoint among subjects with initial FEV_1 35 to 49% predicted is not appropriate because such a trial would have inadequate power to detect smaller yet important mortality differences. More conventional mortality differences (30 to 50%) should be used as effect sizes when designing a trial based on mortality (8).

We have presented calculations for a one-sided test, where the alternative hypothesis of interest is that outcomes improve among subjects receiving augmentation therapy. In the case of intravenous augmentation therapy for α1AT deficiency, compelling evidence of biochemical efficacy and the available observations from prior clinical studies justify considering only the outcome where augmentation therapy slows the rate of FEV_1 decline in recipients. Furthermore, because of the expense of augmentation therapy, it will be accepted only if it is shown to be significantly better than the control.

Although the current updated estimates of required sample size suggest that a randomized controlled clinical trial of intravenous augmentation therapy is more feasible than originally projected (9) when using rate of FEV_1 decline as the outcome measure, other important hurdles to conducting such a trial remain. For example, formidable requirements still include the expense of such a trial, as well as the potential difficulties of recruiting a cohort of individuals with severe α1AT deficiency and established airflow obstruction who would be willing to consent to a randomized trial with a 50% chance of receiving a weekly placebo preparation intravenously. With specific respect to cost, assuming a conservative yearly expense of $20,000 (U.S.) per subject (based on the current drug price and a weekly dose of 60 mg/kg), the cost of providing the drug to 147 antiprotease recipients for 4 yr would be $11.76 million (U.S.). Also, obtaining patient consent may be particularly difficult in the face of observational data from the NHLBI Registry indicating that recipients of augmentation therapy with moderate airflow obstruction experienced a lower rate of decline of lung function and improved survivorship than nonrecipients (11). One final challenge to conducting a large randomized controlled clinical trial is procuring enough pooled human plasma antiprotease to supply study subjects. Currently, only a single preparation of pooled human plasma antiprotease has received FDA approval (Prolastin, Bayer, West Haven, CT) and the total available supply is committed to individuals currently receiving augmentation on their physicians' prescription. Although other preparations of pooled human plasma and recombinant antiprotease are currently being evaluated in FDA-approved research studies, it is currently unlikely that available quantities would suffice to supply the required randomized clinical trial. As a possible offset to these impediments, an encouraging development within the α1AT-deficient patient community since the NHLBI-sponsored Registry has been the organization and commitment by the patient community to facilitate research.

A key decision in designing a clinical trial will be the choice of the primary outcome. Even if a trial is designed using rate of FEV_1 decline as primary outcome, mortality is a harder clinical endpoint and should be included at least as a secondary endpoint, though power to detect important mortality differences on the order of 30 to 50% may not be high (8). It may be wise to increase the sample size to provide minimum acceptable power, e.g., 70%, for the detection of large differences in mortality, e.g., 40%.

With regard to the availability of adequate numbers of untreated α1AT-deficient individuals as prospective participants in a clinical trial, estimates from population-based studies suggest that approximately 100,000 Americans have severe deficiency of α1AT (23), though the majority are undiagnosed. In the NHLBI Registry, which was admittedly not a population-based study, but which nonetheless may be representative of the selected population from which a clinical trial would recruit subjects, 20% of subjects had Stage II COPD at enrollment. Among 756 subjects contacted in the final 12 mo of the NHLBI Registry who had not received lung transplants, 113 patients (15%) had Stage II COPD using their last available measurement of FEV_1 percent predicted, and of these 113, only 37 (33%) were not receiving intravenous augmentation therapy as of last contact in the Registry. These figures suggest that the best source of Stage II COPD subjects not already receiving therapy will be incident cases in which augmentation therapy has not yet been initiated.

Although study designs other than a placebo-controlled trial in subjects with Stage II COPD have been discussed, they too pose significant challenges. For example, subjects might be more willing to enroll in a randomized trial comparing weekly versus monthly intravenous augmentation therapy, rather than in a placebo-controlled trial. However, the effect size would be expected to be smaller in such a trial, thereby requiring greater sample sizes than estimated for a randomized, placebo-controlled trial. Alternatively subjects with less severe COPD, e.g., with initial FEV_1 50 to 79% predicted, might be more amenable to participate in a well-designed placebo-controlled randomized clinical trial. However, data from the NHLBI Registry (11) suggest that the difference in rates of FEV_1 decline between those receiving and not receiving augmentation therapy is smaller in this group of patients (i.e., difference in mean rates of decline of 7.5 ml/yr), which would necessitate larger sample sizes in a clinical trial.

In summary, our calculation of required sample sizes for a placebo-controlled randomized clinical trial of intravenous augmentation therapy using estimates derived from the large NHLBI-sponsored Registry suggests that fewer subjects would be needed than were originally projected when the first commercially available pooled human plasma antiprotease preparation was being evaluated for FDA approval. Although significant obstacles to conducting a placebo-controlled clinical trial still exist, like others (11–14), we recommend a randomized, placebo-controlled clinical trial as the best method to definitively evaluate the efficacy of intravenous augmentation therapy and of possible future treatments.

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APPENDIX

The following institutions and individuals are participants in the Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin. A full list of individuals is provided in Reference 10.

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