Survival and FEV_1 Decline in Individuals with Severe Deficiency of α_1-Antitrypsin

The Alpha-1-Antitrypsin Deficiency Registry Study Group*

Subjects ⩾ 18 yr of age with serum α_1-antitrypsin (α_1-AT) levels ⩽ 11 μM or a ZZ genotype were followed for 3.5 to 7 yr with spirometry measurements every 6 to 12 mo as part of a National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of Alpha-1-Antitrypsin. Among all 1,129 enrollees, 5-yr mortality was 19% (95% CI: 16 to 21%). In multivariate analyses of 1,048 subjects who had been contacted ⩾ 6 mo after enrolling, age and baseline FEV_1% predicted were significant predictors of mortality. Results also showed that those subjects receiving augmentation therapy had decreased mortality (risk ratio [RR] = 0.64, 95% CI: 0.43 to 0.94, p = 0.02) as compared with those not receiving therapy. Among 927 subjects with two or more FEV_1 measurements ⩾ 1 yr apart, the mean FEV_1 decline was 54 ml/yr, with more rapid decline in males, those aged 30 to 44 yr, current smokers, those with FEV_1 35 to 79% predicted, and those who ever had a bronchodilator response. Among all subjects, FEV_1 decline was not different between augmentation-therapy groups (p = 0.40). However, among subjects with a mean FEV_1 35 to 49% predicted, FEV_1 decline was significantly slower for subjects receiving than for those not receiving augmentation therapy (mean difference = 27 ml/yr, 95% CI: 3 to 51 ml/yr; p = 0.03). Because this was not a randomized trial, we cannot exclude the possibility that these differences may have been due to other factors for which we could not control. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of α_1-antitrypsin.

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Alpha-1-antitrypsin (α_1-AT) deficiency is an hereditary disorder characterized by low serum levels of α_1-AT, an increased risk of emphysema at an early age, and less commonly, an increased risk for liver disease, particularly in children (1–3). Individuals with the deficiency lack protection normally provided by α_1-AT against neutrophil elastase released by neutrophils in the lower respiratory tract, leading to destruction of lung parenchyma and to emphysema (4). Currently, the only approved therapy for this disorder is to augment the serum level of α_1-AT, and thereby lung levels of this protein, by weekly intravenous infusions of a purified preparation of human α_1-AT (augmentation therapy [5, 6]). Such therapy has been shown to increase levels of serum and lung α_1-AT and of antineutrophil elastase appropriately (5–7), but its clinical efficacy in improving survival or reducing the rate of decline in lung function has never been demonstrated. We examined decline in FEV_1 and mortality in relation to augmentation therapy and other factors among subjects enrolled in a National Heart, Lung and Blood Institute (NHLBI) Registry of Patients with Severe Deficiency of α_1-AT.

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* A full list of institutions and investigators participating in this Registry is provided in the APPENDIX.

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METHODS

Study Design

The Registry was initiated in 1988 as a means of collecting information on the natural history of α_1-AT deficiency, after sample sizes for a randomized clinical trial of augmentation therapy were deemed infeasible to obtain (8, 9). Details of study design and baseline characteristics have been described previously (10, 11). The Registry protocol was reviewed and approved by the appropriate institutional review board at each of the 37 participating clinical centers. Eligible subjects were ⩾ 18 yr of age and either had serum α_1-AT levels ⩽ 11 μM, confirmed by a central laboratory (n = 1,026), or a ZZ genotype, confirmed by DNA gene-probe analysis (n = 103). From March 1989 through October 1992, 1,129 eligible subjects were enrolled from 37 centers. Follow-up continued through April 1996, with individuals returning for annual or semiannual visits. Spirometry was performed before and after bronchodilator treatment, using a standard protocol (10). As previously described, great attention was given to assuring high-quality, reproducible spirometry results, and baseline FEV_1 measurements achieved high reproducibility rates for both prebronchodilator (95.0%) and postbronchodilator (95.7%) measurements (12). Smoking status was based on subjects' self-reports. The baseline (initial) smoking status was examined in relationship to survival, and current (last reported) smoking status was examined in relationship to FEV_1 decline. Dosing frequency of augmentation therapy was self-reported by the subject and was verified with augmentation-therapy logs when available. Regular medical care for participants may have been provided by physicians not associated with the Registry. If a subject was unable to return for a follow-up visit, a telephone-contact form was used to ascertain vital status and collect updated information on use of augmentation therapy. The National Death Index (National Center for Health Statistics, Hyattsville, MD) and Equifax, Inc. (McLean, VA) were used to search for unreported deaths. A Death Review Committee reviewed available records to ascertain causes of death.

Use of Augmentation Therapy

Augmentation therapy refers to the intravenous infusion of purified, pooled human α_1-AT (5–7, 13–16). The α_1-AT preparation Prolastin (Bayer, Inc., West Haven, CT), currently the only commercially available preparation, has been approved by the U.S. Food and Drug Administration (FDA) for once weekly use at 60 mg/kg. Decisions about treatment with intravenous α_1-AT were made by the participants' physicians, not by the Registry. Logs recording use of augmentation therapy were completed by the subjects and turned in at clinic visits. Subjects were also questioned about augmentation therapy at regular visits or, when they were unable to come in for regular visits, by telephone. Subjects were classified as always, partly, or never receiving α_1-AT augmentation therapy while in the Registry. The "always receiving" therapy group included those on therapy continuously, beginning at or within 3 mo of enrollment. The "partly" on therapy group included those who began therapy $>$ 3 mo after enrollment or who discontinued therapy for $>$ 1 mo after enrollment. Classifications of "always," "partly" and "never" receiving therapy were made irrespective of dosing frequency, which was determined by the subjects' managing physicians. Measurement of "trough" serum α_1-AT levels in augmentation-therapy recipients was not required. Although these measurements were recorded when submitted, they were infrequently available.

Statistical Analysis

Continuous distributions were compared through Wilcoxon's rank-sum test, and categorical variables were compared through the chi-square test.

Survival. For statistical analysis of survival from the time of enrollment, we used the Kaplan–Meier method (17), the log-rank test (18), and Cox's proportional hazards regression (19). Survival times of subjects receiving liver transplants were censored at the time of transplantation, and receipt of a lung transplant was treated as a time-varying covariate. The baseline or first available postbronchodilator measurement of FEV_1% predicted was used as a covariate in the survival models, using American Thoracic Society (ATS) staging strata (20) (i.e., FEV_1% predicted $<$ 35% [Stage III], 35 to 49% [Stage II], 50 to 79% [Stage I], and $\geq$ 80% [Normal]). Mortality was compared among groups never, partly, and always receiving augmentation therapy, and also by using a time-varying covariate, classifying each subject as receiving or not receiving therapy at each time point. To reduce the possibility of bias toward a positive effect of augmentation therapy caused by including subjects who were not on therapy at enrollment and who later died before returning for a follow-up visit (and presumably before they could begin augmentation therapy), a "landmark analysis" (21) was performed, including only subjects who were contacted $\geq$ 6 mo after enrollment.

Decline in FEV_1. Analyses of decline in FEV_1 included subjects with two or more postbronchodilator FEV_1 measurements obtained $\geq$ 1 yr apart. FEV_1 measurements obtained following lung or liver transplants were excluded from all analyses. Rates of FEV_1 decline were estimated for individual subjects through least-squares regression of FEV_1 versus time since enrollment. We analyzed decline in FEV_1 with a linear mixed-effects model (22), in which the responses were the changes in FEV_1 between the first available measurement and all available subsequent measurements, with random effects for individual subjects' intercepts and rates of FEV_1 decline. The mean FEV_1% predicted, calculated from all available visits, was used as a covariate, rather than using initial FEV_1% predicted, in order to avoid problems of regression to the mean (23). Bronchodilator responsiveness, coded as whether the subject ever versus never had a bronchodilator response (defined as postbronchodilator increase in FEV_1 of at least 200 ml and 12% over the prebronchodilator value [20, 24]) at any visit, was examined as a covariate. The cumulative time (since enrollment) for which each subject had received augmentation therapy at each follow-up visit was included in the model as a time-dependent covariate, allowing estimation of the average rates of decline in FEV_1 while receiving and not receiving augmentation therapy. We also used a simpler approach, classifying subjects as either always or never receiving therapy in the mixed-effects model. In this approach, FEV_1 data from subjects partly receiving therapy were used for the period during which they were continuously receiving or not receiving therapy, whichever was the longer period, provided that this period was $\geq$ 1 yr. The nonlinear relationship between decline in FEV_1 and FEV_1% predicted was examined in the mixed-effects model by modeling FEV_1% predicted with cubic polynomial splines (25). Values are reported as means $\pm$ 1 SD; all reported p values are two-tailed, without adjustment for multiple comparisons.

RESULTS

Of the 1129 subjects in the study, 204 (18.1%) expired (including 11 who had previously dropped out), 39 (3.5%) dropped out, and 886 (78.5%) remained in the study as of April 30, 1996. The multivariate survival analysis excluded 76 subjects (54 deaths) who did not have follow-up contact $\geq$ 6 mo after enrollment, and five subjects (one death) because data for initial FEV_1% predicted or education were missing. Deaths following liver transplantation were censored, leaving 1,048 subjects and 147 deaths used in the analysis. The analyses of FEV_1 decline excluded 202 subjects who did not have at least two postbronchodilator FEV_1 measurements, obtained at least 1 yr apart (76 of whom were also excluded from the survival analysis because of lack of follow-up contact $\geq$ 6 mo after enrollment.

Follow-up

Among subjects eligible to return for each annual visit, rates of return for follow-up visits were 80%, 75%, 72%, 71%, and 69%, respectively, for visits in the first through fifth years. Rates of contact by visit or telephone ranged between 81 and 84% for the first through fifth years. Six hundred ninety (78%) of the 886 subjects remaining in the study in April 1996 had returned for a follow-up visit in the year immediately preceding, and 807 (91%) were contacted (visit or phone) in that same year.

Transplants and Chest Surgeries

There were 74 single-lung, 37 double-lung, one heart/lung, and seven liver-transplant recipients among Registry subjects. All liver transplants and 106 of 112 (95%) of the lung transplants were performed after enrollment. Twenty additional subjects underwent lung surgery after enrollment, 19 with resections (17 with bullectomy or lung-volume-reduction surgery).

Use of Augmentation Therapy

Among the 1,129 subjects enrolled in the study, 382 (34%) never received augmentation therapy, 390 (35%) always received therapy, and 357 (32%) were partly receiving therapy while in the Registry. When this evaluation was restricted to subjects included in the analysis of FEV_1 decline (Table 1), 277 (30%) never, 389 (42%) always, and 261 (28%) partly received augmentation therapy while in the Registry. Of the 357 subjects classified as partly receiving therapy, 55% started augmentation therapy $>$ 3 mo after enrollment, 38% permanently discontinued therapy, and 7% temporarily stopped and then restarted therapy. The 357 subjects classified as partly receiving therapy were followed for a total of 20,564 mo in the Registry, and were receiving augmentation therapy for 13,627 mo, or 66% of the total period. Reported reasons for permanently discontinuing augmentation therapy were receipt of a lung transplant (80 of 137 subjects; 59%), financial constraints (16 of 137 subjects; 12%), adverse reactions ascribed to augmentation therapy (four of 137 subjects; 3%), and other/unknown causes (37 of 137 subjects; 27%). Among those never receiving augmentation therapy, predominant reasons for not starting therapy included: not recommended by physician because of normal lung function (54%); cost (17%); receipt or anticipation of a lung transplant (6%); not recommended by

TABLE 1

BASELINE CHARACTERISTICS OF SUBJECTS BY AUGMENTATION THERAPY FOR SUBJECTS INCLUDED IN SLOPE ANALYSIS AND FOR THOSE EXCLUDED FROM SLOPE ANALYSIS

	Included in Slope Analysis, by Augmentation-therapy Status*				Excluded from Slope Analysis (*n = 202*)
	Never Receiving (*n = 277*)	Partly Receiving (*n = 261*)	Always Receiving (*n = 389*)	All Subjects (*n = 927*)	
Males, %	49.1	57.9	58.1	55.3	56.4
Deaths, % (n)	8.7 (24)	12.6 (33)	11.8 (46)	11.1 (103)	50.0 (101)
Never smoked, %	40.8	15.7	11.3	21.4	14.4
Ex-smokers, %	49.8	73.6	83.3	70.6	76.2
Current smokers,%	9.4	10.7	5.4	8.1	9.4
Ascertainment, %					
Pulmonary symptoms, %	46.9	80.5	82.8	71.4	76.2
Family screening, %	41.2	13.0	11.6	20.8	14.9
Other, %	11.9	6.5	5.7	7.8	8.9
FEV_1, % predicted					
$< 35\%$	24.2	46.4	55.5	43.6	66.8
35–49%	9.0	27.2	25.7	21.1	16.3
50–79%	14.1	20.3	14.9	16.2	6.1
$\geq 80\%$	52.7	6.1	3.9	19.1	10.7
Bronchodilator response at initial visit, %†	18.1	36.4	34.2	30.0	15.0
Age at enrollment, mean ± SD	43 ± 12	47 ± 10	47 ± 9	46 ± 11	48 ± 10
FEV_1, % predicted (mean ± SD)	74 ± 35	41 ± 21	37 ± 18	49 ± 30	36 ± 27
FEV_1, ml (mean ± SD)	2,651 ± 1,438	1,447 ± 752	1,306 ± 671	1,748 ± 1,147	1,259 ± 1,018
Serum α_1-AT, μM (mean ± SD)	5.8 ± 1.5	5.6 ± 1.4	5.7 ± 1.3	5.7 ± 1.4	6.1 ± 1.2
Follow-up, months; median (range)	51 (12–82)	55 (12–86)	50 (12–84)	52 (12–86)	0 (0–11.96)
Number of data points, median (range)	5 (2–13)	6 (2–12)	6 (2–12)	5 (2–13)	1 (1–3)
Education $\geq$ 12th grade, %	87.4	91.9	92.5	90.8	88.1
Family income $\geq$ $50,000/year, %‡	20.2	28.5	33.3	28.3	17.7
With insurance coverage, %‡	88.0	90.4	97.3	92.6	97.1

* Patients included in the slope analysis were those with at least two postbronchodilator FEV_1 measurements obtained $\geq$ 1 yr apart (not counting measurements obtained after lung or liver transplantation.

† Bronchodilator response defined as an increase in FEV_1 of at least 12% and 200 ml postbronchodilator.

‡ Family income, insurance coverage based on n = 687 and 767 subjects with data, respectively.

physician because of poor lung function (5%); and presence of a medical contraindication (5%), with 13% other/unknown.

Initial dosing frequencies were 383 (51.3%) weekly, 189 (25.3%) biweekly, and 163 (21.8%) monthly, with 12 (1.6%) unknown. Over time, frequencies changed such that among 633 subjects who had multiple reports of dosing frequency, at last report, 33% were receiving weekly, 43% biweekly, and 24% monthly therapy. Also, 66% of subjects had not changed dosing frequency, 25% had decreased frequency (18% from weekly to biweekly, 5% from weekly to monthly, 2% from biweekly to monthly), and only 9% had increased the frequency of infusion (2% from monthly to weekly, 4% from monthly to biweekly, 3% from biweekly to weekly). Of these 633 subjects, the numbers of subjects who remained on a fixed dosage interval for $\geq$ 90% of the time they were receiving therapy were 168 (26.5%) on weekly, 158 (25.0%) on biweekly, and 118 (18.6%) on monthly dosages; another 189 (29.9%) were not on a constant dosage for $\geq$ 90% of the time.

Baseline Characteristics

The 927 subjects included in the analysis of FEV_1 (Table 1) had a mean age of 46 yr; 55% were male, 71% were ex-smokers, and the subjects' mean FEV_1 was 49 ± 30% predicted. Most (71%) were ascertained because they had pulmonary symptoms. Compared with those who received augmentation therapy, subjects who never received augmentation therapy were more likely to have $FEV_1 \geq 80\%$ predicted (53%, versus 6% and 4% for those partly and always receiving therapy, respectively), were less likely to be ascertained because of pulmonary symptoms, had lower family income, and were less likely to have insurance coverage (Table 1).

Compared with the 927 subjects included in the FEV_1 analysis, the 202 subjects excluded did not differ significantly with respect to gender, smoking, ascertainment method, education, income, or insurance coverage (Table 1). However, subjects excluded from the analysis had more severe airflow obstruction at baseline, with a mean FEV_1% predicted of 36 ± 27%, as compared with 49 ± 30% for subjects included in the analysis ($p \leq 0.0001$), and also were older ($p = 0.0008$), had higher serum α_1-AT levels ($p = 0.04$), and were less likely to exhibit a bronchodilator response at the initial visit ($p \leq 0.001$).

Survival

The mean length of follow-up of survivors was 57 ± 17 mo. Kaplan–Meier estimates ± SE of cumulative mortality for the entire Registry cohort at 3 and 5 yr after enrollment were 10.5 ± 0.9% and 18.6 ± 1.3%, respectively. As has been previously shown (20, 26, 27), initial FEV_1% predicted was a major determinant of survival; for example, 5-yr Kaplan–Meier mortality rates (± SE) were 30.3 ± 2.2%, 12.0 ± 2.4%, and 4.3 ± 1.2%, respectively, among subjects with an initial FEV_1% predicted of $\leq$ 35% (n = 535), 35 to 49% (n = 228), and $\geq$ 50% (n = 360) (log-rank p value ≤ 0.001).

Among all subjects with initial $FEV_1 < 50\%$ predicted (Figure 1A), mortality was significantly higher ($p \leq 0.001$) for subjects who never as opposed to sometimes or always received augmentation therapy. Mortality rates were low for subjects with initial $FEV_1 \geq 50\%$ predicted (Figure 1B), and did not differ between augmentation-therapy groups. Similar results were seen when the analysis was restricted to subjects having follow-up contact $\geq$ 6 mo after enrollment (Figures 1C and D).

In multivariate analyses based on 1,048 subjects (147 deaths)

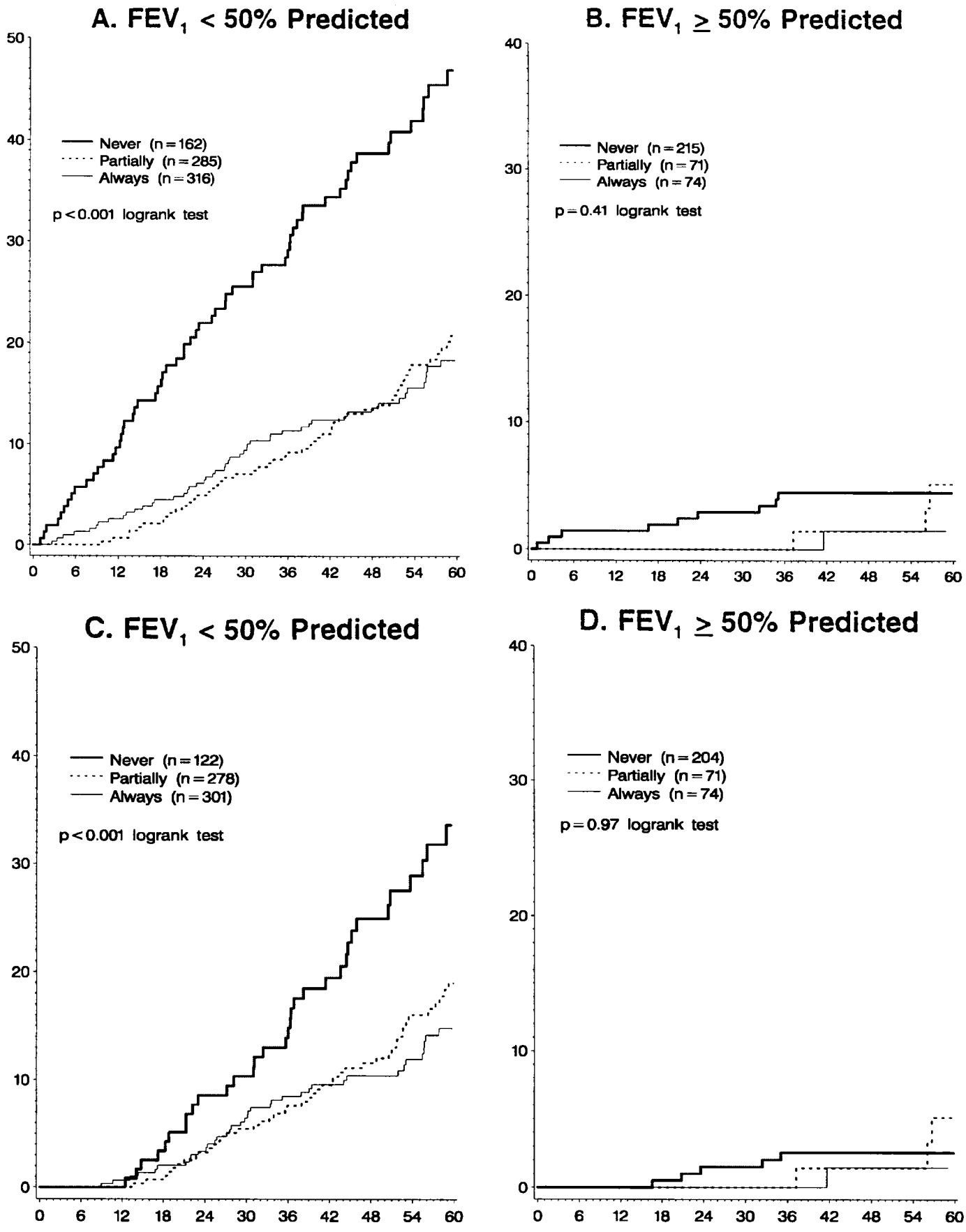

Figure 1. Kaplan–Meier cumulative mortality curves based on all eligible patients and deaths, plotted for subjects with initial $FEV_1 < 50\%$ predicted and for those with initial $FEV_1 \geq 50\%$ predicted. In each plot, separate curves are shown for subjects classified as never receiving (*thick solid line*), partly receiving (*dotted line*), and always receiving (*narrow solid line*) augmentation therapy. The log-rank p value presented is for a comparison of the subjects never receiving therapy with the combined group of subjects partly or always receiving therapy. (*A* and *B*) Kaplan–Meier plots of survival from time of enrollment using data from all subjects. (*C* and *D*) Similar analysis, but restricted to those subjects who had follow-up contact for at least 6 mo after enrolling in the Registry.

with follow-up contact ⩾ 6 mo after enrollment (Table 2), increased age, lower education, lower FEV_1% predicted, receipt of a lung transplant, and not receiving augmentation therapy (modeled as a time-varying covariate) were all significantly associated with increased mortality risk. In addition, gender was included in all multivariate models even though it was not a significant predictor of mortality. When adjustment was made for gender and the other significant predictors, mortality risk was significantly lower among subjects receiving augmentation therapy than among those not receiving therapy (risk ratio [RR] = 0.64; 95% CI = 0.43 to 0.94; p = 0.02; Table 2). In addition, the interaction between FEV_1% predicted and use of augmentation therapy was statistically significant (p = 0.01; Table 2, Footnote 2), indicating that the effect of augmentation therapy differed across strata of FEV_1. We therefore examined the effect of augmentation therapy on survival separately by level of FEV_1% predicted, as well as for the entire group. Use of augmentation therapy was associated with lower mortality in the subgroup with initial FEV_1 values of 35 to 49% predicted (ATS Stage II) (RR = 0.21, 95% CI = 0.09 to 0.50, p ⩽ 0.001).

When added to the multivariate model including gender and other significant predictors, ascertainment method (ascertained on the basis of symptoms, family screening, or other basis), serum α_1-AT as a continuous variable, bronchodilator response at the initial visit (yes/no), and initial smoking status (never/ex-/current smoker) were not significantly related to survival. In similar analyses, oxygen use (i.e., ever receiving oxygen ⩾ 12 hr/d while enrolled) was associated with increased mortality (RR = 1.46, p = 0.04), but the association between augmentation therapy and survival remained statistically significant. Further adjustment for clinical centers (n = 1) found to have significantly higher mortality than other centers, or for centers with poorer follow-up rates (n = 8 centers with < 80% follow-up in the final year), did not alter the findings with respect to augmentation therapy.

Similar results were obtained with an alternative approach to modeling augmentation therapy; in proportional hazards regressions adjusting for the same covariates as in Table 2, mortality risk ratios in comparisons of subjects who sometimes or always as opposed to those who never received augmentation therapy were 0.67 (p = 0.04) among all subjects, and 0.29 (p = 0.005) for subjects with initial FEV_1 values of 35 to 49% predicted. Additionally, initial frequency of therapy was not related to survival in subjects receiving therapy after adjustment for factors in the multivariate model (p > 0.10).

Analyses were also repeated with survival times of lung-transplant recipients censored at the time of transplant, rather than using lung transplantation as a covariate in the model, and findings were unchanged. A detailed examination of survival of transplant recipients will be the subject of a separate report.

In analyses restricted to subjects with follow-up contact ⩾ 12 mo after-enrollment (1,020 subjects; 125 deaths), the pooled RRs for augmentation therapy from the two modeling approaches (i.e., using a time-varying covariate to compare those receiving versus not receiving augmentation therapy, and using the second statistical model, which compared subjects who sometimes or always received therapy with those who never received therapy), with control for age, gender, education, and transplant status, were 0.63 (p = 0.04) and 0.70 (p = 0.10), respectively.

Among 118 deaths for which sufficient information was available to determine cause of death, predominant underlying causes of death were emphysema (n = 85; 72%) and cirrhosis (n = 12; 10%), followed by malignancy (n = 3), diverticulitis (n = 2), sepsis/infection (n = 2), and trauma/accident (n = 2). Twelve other causes accounted for a single death each.

Decline in FEV_1

The average rate of decline in FEV_1 among all 927 subjects was 54 ml/yr. Histograms of rates of FEV_1 decline for individ-

TABLE 2

MULTIVARIATE SURVIVAL ANALYSIS*†

Variable	Category	Subjects	Deaths	RR	95% CI	p Value
Gender	Male	579	85	1.01	(0.72, 1.41)	0.96
	Female	469	62	1	—	
Age	⩾ 65	56	18	5.61	(3.26, 9.67)	< 0.001
	55–64	156	38	2.80	(1.89, 4.16)	
	< 55	836	91	1	—	
Education, yr	< 12	94	28	2.73	(1.47, 5.06)	< 0.001
	12	360	54	1.30	(0.75, 2.27)	
	13–16	439	48	0.96	(0.55, 1.67)	
	> 16	155	17	1	—	
Lung transplant	Yes	105	35	3.62	(2.15, 6.11)	< 0.001
	No	943	112	1	—	
Initial FEV_1	< 35%	482	114	7.25	(3.78, 13.88)	< 0.001
	35–49%	217	22	3.23	(1.54, 6.80)	
	⩾ 50%	349	11	1	—	
Augmentation Therapy						
Overall	Never on	326	41	1	—	0.02
	Ever on	722	106	0.64	(0.43, 0.94)	
FEV_1 < 35%	Never on	90	25	1	—	0.44
	Ever on	392	89	0.83	(0.52, 1.33)	
FEV_1 35–49%	Never on	32	10	1	—	< 0.001
	Ever on	185	12	0.21	(0.09, 0.50)	
FEV_1 ⩾ 50%	Never on	204	6	1	—	0.64
	Ever on	145	5	0.75	(0.22, 2.56)	

* The analysis excludes subjects with no follow-up contact ⩾ 6 mo after enrolling.

† All risk ratios (RRs), with the exception of those for initial FEV_1% predicted and overall augmentation therapy, were obtained by fitting a proportional hazards model that included all covariates as well as the interaction between FEV_1 and augmentation therapy. RRs for initial FEV_1 and overall augmentation therapy were obtained from a model that excluded the FEV_1 by augmentation therapy interaction. Lung transplant and augmentation therapy (receiving versus not receiving) were modeled as time-varying covariates. The interaction between FEV_1 and augmentation therapy was statistically significant (p = 0.01).

ual subjects (Figure 2) confirmed that the majority of subjects, both receiving and not receiving augmentation therapy, experienced a decline in FEV_1. In univariate analyses (Table 3), statistically significant differences in mean rates of FEV_1 decline were seen by gender, age, current smoking status, serum α_1-AT level, mean FEV_1% predicted, and ever versus never having a bronchodilator response.

In multivariate analyses, significant predictors of decline in FEV_1 (Tables 4 and 5) included gender, age, current smoking status, bronchodilator response, and mean FEV_1% predicted. Because the effect of augmentation therapy differed across levels of mean FEV_1% predicted ($p = 0.05$), effects of augmentation therapy were examined separately by category of FEV_1% predicted, as well as for the overall cohort. Serum α_1-AT level was significant in the multivariate model (Table 5); however, it was not included in the final model because to do so would have excluded 79 subjects with missing serum α_1-AT levels, and its inclusion in the model did not substantially alter the results. Income, insurance coverage, and education were not significantly related to FEV_1 decline in the multivariate analyses. Occupational exposure to dust or fumes, defined as any prior exposure and also as any exposure while enrolled in the Registry, was not significantly related to FEV_1 decline. Among all subjects, mean rates of FEV_1 decline did not differ for those receiving versus those not receiving augmentation therapy (Table 5) (difference in means = 4 ml/yr, $p = 0.40$). However, among subjects with mean FEV_1 values of 35 to 49% predicted (Stage II), the rate of FEV_1 decline was slower for those receiving than for those not receiving augmentation therapy (difference in means = 27 ml/yr, 95% CI: 3 to 51 ml/yr, $p = 0.03$). For Stage I and II subjects combined (i.e., FEV_1 of 35 to 79% predicted), the mean difference in rates of decline when receiving versus not receiving augmentation therapy was 14 ml/yr (95% CI: −4 to 31 ml/yr; $p = 0.13$). In keep-

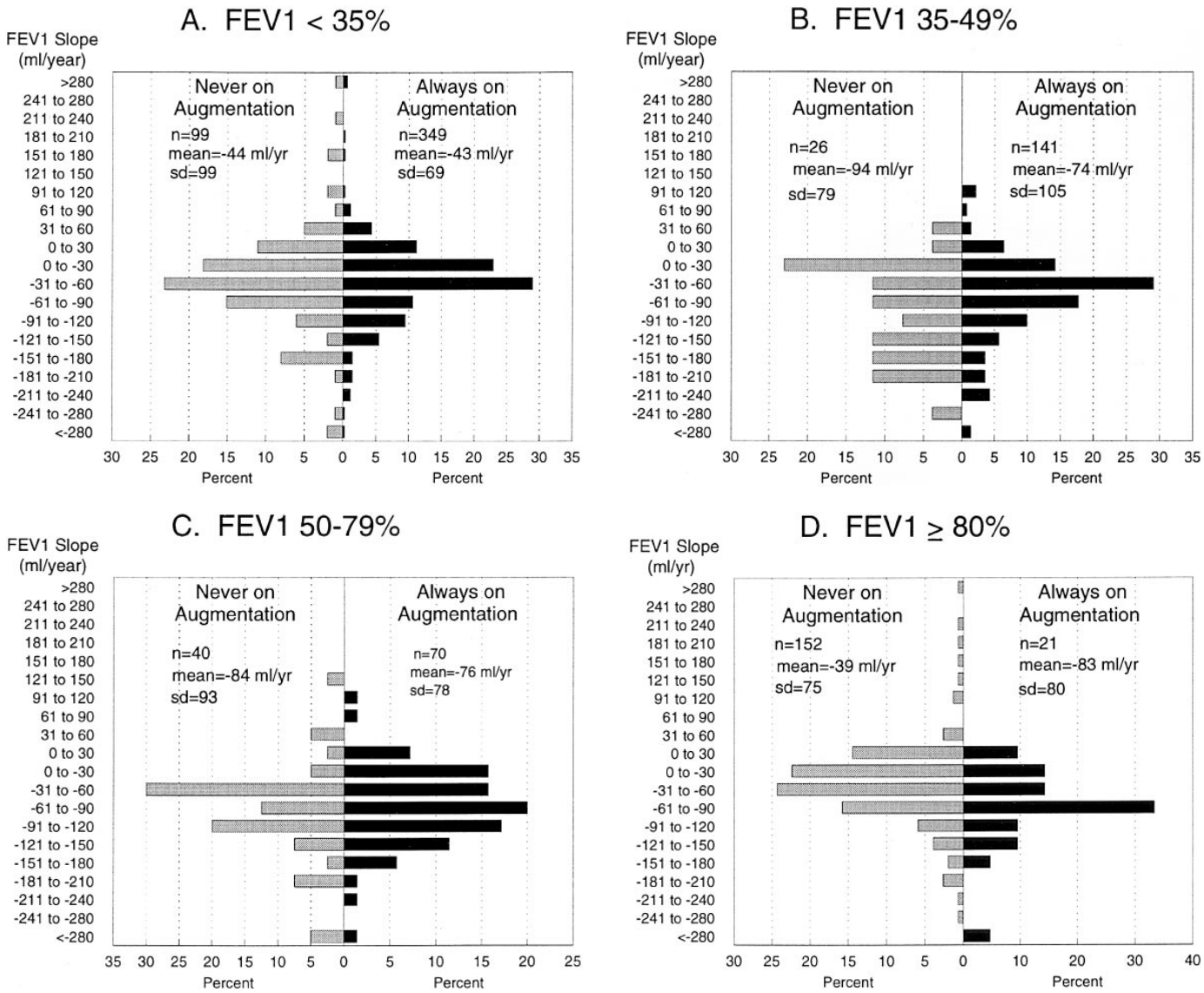

Figure 2. Histograms of individual rates of FEV_1 decline, by augmentation-therapy status and mean FEV_1% predicted. Shown is the distribution of the individual least-squares slopes (ml/yr) calculated for individual Registry subjects. These plots include only those subjects who had two or more postbronchodilator measurements of FEV_1 at least 1 yr apart while they were continuously receiving or not receiving augmentation therapy. For subjects who were both receiving and not receiving augmentation therapy while in the Registry, the data from the longer period (receiving or not receiving therapy) were used to calculate a slope; the other data were excluded for the purpose of this analysis.

TABLE 3

UNIVARIATE ANALYSIS OF FEV_1 DECLINE

Variable	Category	n	Mean Decline (*ml/yr*)	SE	p Value
Entire group		927	−54.3	2.1	—
Gender	Male	513	−63.0	2.8	< 0.001
	Female	414	−43.5	3.1	
Current smoking status	Never smoked	208	−57.5	4.3	< 0.001
	Ex-smoker	697	−52.0	2.4	
	Current smoker	22	−108.2	15.0	
Ascertainment	Symptoms	662	−54.5	2.5	0.38
	Family	193	−50.5	4.5	
	Other	72	−63.4	7.3	
Bronchodilator responder at any visit*	No	421	−40.2	3.1	< 0.001
	Yes	506	−64.6	2.7	
Mean FEV_1% predicted	< 35%	460	−44.6	3.0	< 0.001
	35–49%	176	−72.2	4.5	
	50–79%	118	−75.7	5.5	
	⩾ 80%	173	−43.8	4.6	
Serum α_1-AT level, μM	< 5.7	456	−61.1	2.9	< 0.001
	⩾ 5.7	392	−46.3	3.3	
Enrollment age, yr	< 30	37	−34.9	10.2	< 0.001
	30–44	424	−65.1	3.0	
	45–54	284	−47.0	3.7	
	55–64	135	−43.8	5.5	
	⩾ 65	47	−46.7	9.4	

* Subjects were classified as to whether they ever or never experienced a bronchodilator response, defined as an increase in FEV_1 of at least 12% and 200 ml following bronchodilator administration at any Registry visit.

ing with an earlier subgroup analysis by Buist and colleagues (28), we also examined the subgroup with a mean FEV_1 of 30 to 64% predicted. This analysis showed a decreased rate of FEV_1 decline for those receiving augmentation therapy (difference in means = 18 ml/yr, 95% CI: 2 to 34 ml/yr; p = 0.03). Similar results were obtained when the analysis was done on an expanded cohort of 979 subjects, obtained by including an additional 52 subjects who had two or more postbronchodilator FEV_1 measurements that were less than 1 yr apart.

The analyses were repeated with adjustment for the baseline rather than the mean FEV_1% predicted, yielding similar results. The interaction between augmentation and initial FEV_1% predicted approached statistical significance (p = 0.06). In Stage II subjects (initial FEV_1 of 35 to 49% predicted), FEV_1 decline was slower for those receiving than for those not receiving augmentation therapy (difference in means = 22 ml/yr, p = 0.04). In an analysis of change in FEV_1/height^3, conducted to adjust for body size, gender and bronchodilator responsiveness were not statistically significant, whereas age and smoking status remained significant. Among Stage II subjects the decline in FEV_1/height^3 was less for those receiving than for those not receiving augmentation therapy (p = 0.04).

In multivariate analyses, average rates of FEV_1 decline among subjects always receiving therapy did not differ significantly among those always receiving weekly, biweekly, monthly, or other regimens (p > 0.10).

The relationship between FEV_1 decline and mean level of FEV_1% predicted, estimated through cubic spline techniques separately for those receiving versus those not receiving augmentation therapy (Figure 3A), appears U-shaped. Differences in mean rates of decline with and without augmentation therapy (Figure 3B) suggest that among subjects with an FEV_1 in the range of 20 to 80% predicted, those receiving augmentation therapy tended to have a slower decline in FEV_1. This trend appears to have reversed for subjects with FEV_1 values above 80% predicted (Table 5), although the number of such subjects receiving augmentation therapy was quite small (n = 21; Figure 2D).

TABLE 4

MULTIVARIATE ANALYSIS OF FEV_1 DECLINE: MEAN FEV_1 DECLINE (ml/yr) BY GENDER, SMOKING STATUS, AGE, AND BRONCHODILATOR RESPONSE*

Variable	Category	Mean	95% CI	p Value
Gender	Male	−65.8	(−74.2, −57.3)	< 0.001
	Female	−49.8	(−59.0, −40.6)	
Smoking status	Never smoker	−67.2	(−78.4, −56.0)	< 0.001
	Ex-smoker	−54.6	(−62.9, −46.3)	
	Current smoker	−108.8	(−136.7, −80.9)	
Age, yr	< 30	−43.4	(−64.2, −22.7)	< 0.001
	30–44	−71.2	(−80.1, −62.3)	
	45–54	−51.8	(−61.4, −42.2)	
	55–64	−43.0	(−55.4, −30.6)	
	⩾ 65	−39.5	(−58.2, −20.7)	
Bronchodilator response	Ever	−63.5	(−72.3, −54.8)	0.01
	Never	−52.2	(−61.7, −43.4)	

* Reported means are least-squares means that adjust for other factors included in the model. The multivariate model for change in FEV_1 includes gender, smoking status, age, bronchodilator responsiveness, FEV_1% predicted (categorized as < 35%, 35–49%, 50–79%, ⩾ 80%), augmentation-therapy status, and the interaction between FEV_1% predicted and augmentation-therapy status. Estimated means for levels of a variable (e.g., gender) represent the average rates of FEV_1 decline for subjects not receiving augmentation therapy, averaged across the levels (categories) of the other factors (e.g., smoking status, age, bronchodilator responsiveness and FEV_1% predicted), using weights based on the frequencies of these categories in the overall cohort. Reported p values are for comparing the means across categories of each variable, after adjusting for the other variables in the model.

DISCUSSION

In interpreting our findings, two important limitations of this study must be considered. First, the Registry is not a population-based study, and our findings may not be generalizable to the universe of individuals severely deficient in α_1-AT. Second, decisions about treatment with intravenous augmentation therapy were made by the managing physicians of participants. Thus, differences in outcomes between individuals receiving

TABLE 5

MULTIVARIATE ANALYSIS OF FEV_1 DECLINE: MEAN FEV_1 DECLINE (ml/yr) BY FEV_1% PREDICTED AND AUGMENTATION THERAPY STATUS*

	Not Receiving Augmentation Therapy		Receiving Augmentation Therapy		Difference In Slopes: Receiving Versus Not Receiving Augmentation Therapy†		
Mean FEV_1% Predicted	Mean	SE	Mean	SE	Estimate	95% CI	p Value
$FEV_1 < 35\%$	−46.5	6.2	−43.9	3.4	2.6	(−11.3, 16.5)	0.71
FEV_1 35–49%	−93.2	11.1	−66.4	5.0	26.8	(2.8, 50.9)	0.03
FEV_1 50–79%	−81.2	8.9	−73.7	6.8	7.5	(−14.7, 29.6)	0.50
$FEV_1 \geq 80\%$	−39.2	5.6	−63.0	12.8	−23.8	(−50.9, 3.3)	0.09
Pooled categories‡							
All subjects	−56.0	3.8	−51.8	2.7	4.2	(−5.7, 14.2)	0.40
35–79%	−83.5	7.6	−69.9	4.1	13.6	(−4.1, 31.1)	0.13

* Reported means are least-squares means that adjust for other factors included in the model. The multivariate model for change in FEV_1 includes gender, current smoking status, age, bronchodilator responsiveness, FEV_1% predicted (categorized as < 35%, 35–49%, 50–79%, ⩾ 80%), augmentation-therapy status, and the interaction between FEV_1% predicted and augmentation-therapy status. Reported means are the average estimated rates of FEV_1 decline with and without augmentation therapy by level of the mean FEV_1% predicted, averaged across the levels (categories) of the other factors (smoking status, age, bronchodilator responsiveness), using weights based on the frequencies of these categories in the overall cohort.

† A positive difference in slopes implies a slower rate of decline for subjects receiving augmentation therapy compared with those not receiving augmentation therapy. Average slopes with and without augmentation therapy were estimated using cumulative time on augmentation therapy as a time-varying covariate in the mixed-effects model (*see* METHODS section).

‡ Estimates for pooled categories are obtained from a model fit to the entire cohort or to the specific subgroup, with interaction terms between FEV_1% predicted and augmentation therapy excluded from the model.

and those not receiving augmentation therapy may be biased by systematic differences between these groups, and there is no assurance that statistical modeling will completely account for these imbalances. For example, other factors, such as intensity of care received, may be associated with augmentation therapy, and could confound the relationship between use of augmentation therapy and survival or FEV_1 decline.

With these limitations kept in mind, our findings suggest a relationship between intravenous α_1-AT augmentation therapy and improved survival. Although no overall effect of augmentation therapy was found on rate of FEV_1 decline, we found a slower rate of FEV_1 decline in individuals with FEV_1 values of 35 to 49% predicted. These observations buttress the rationale for intravenous augmentation therapy for individuals with α_1-AT deficiency, which up to now has been based mainly on reports demonstrating the "biological efficacy" of intravenous augmentation therapy (5–7).

The observed overall yearly mortality rate of approximately 3.5% in the Registry is consistent with estimates based on earlier studies. Among 246 adult ZZ homozygotes followed for as long as 14 yr, Larsson (29) reported an overall mortality rate of 37% (91 of 246). Wu and Eriksson (26) reported a crude mortality rate of 41% (65 of 158) for 158 ZZ homozygous adults followed for as long as 19 yr. Most recently, Seersholm and colleagues (27, 30, 31) reported a crude mortality rate of 28% among 397 individuals with severe α_1-AT deficiency in the Danish Registry over a median of 5.6 yr of follow-up. Our finding that the most common underlying causes of death among Registry subjects were emphysema (72%) and cirrhosis (10%) confirm Larsson's (29) findings that the predominant causes of death among 91 adult ZZ homozygotes were respiratory insufficiency (59%) and complications of liver cirrhosis (13%).

These results extend results of earlier studies (2, 26, 28, 31–33) which have reached widely varying estimates of the rate of FEV_1 decline in individuals with α_1-AT deficiency. Because of the Registry's large sample size, prospective design, long-term follow-up, and quality-assurance measures, we believe that the rates of FEV_1 decline reported here represent the most accurate available estimates, subject to limitations stated earlier. Estimates of FEV_1 decline for 161 subjects in the Danish Registry (30) who never received augmentation therapy (132 ml/yr for current smokers, 58 ml/yr for ex-smokers, and 86 ml/yr for never smokers) are similar to those reported here. This close agreement between two large cohorts of α_1-AT deficient individuals strengthens confidence in our estimates.

Features we found associated with more rapid decline in FEV_1 included: male gender, current smoking, age 30 to 44 yr, FEV_1 of 35 to 79% predicted, ever having had a bronchodilator response, decreased serum α_1-AT level, and nonuse of augmentation therapy. The greater FEV_1 decline observed in those subjects with bronchodilator responses is of interest, suggesting a link between pathogenesis of disease and the presence of airway hyperresponsiveness (AHR). Although the ascertainment method was not associated with FEV_1 decline, "index cases" (i.e., subjects identified because of symptoms of chronic obstructive pulmonary disease [COPD]) did have more severe airflow obstruction at baseline than did "nonindex" participants (generally identified as family members of affected individuals). In this regard, the Registry confirms previous observations (34).

Prior data relating the effect of augmentation therapy to the rate of FEV_1 decline in α_1-AT deficient individuals are sparse. In a retrospective analysis of the German registry (35), 27 of 323 recipients of augmentation therapy (8%) reported experiencing fewer bronchitic episodes after augmentation therapy was implemented. In this subset of patients, the rate of FEV_1 decline was slower (130 ± 467 ml/yr [mean ± SD]) than the rate of FEV_1 decline among participants for whom the rate of bronchitic episodes did not change (246 ± 352 ml/yr). Also, a recently published comparison of the rate of FEV_1 decline among 97 Danish α_1-AT-deficient ex-smokers not receiving augmentation therapy versus 198 German α_1-AT-deficient ex-smokers receiving augmentation therapy (36) showed a significantly lower rate of FEV_1 decline among the recipients of augmentation therapy (53 ml/yr) than among the nonrecipients (75 ml/yr, $p = 0.02$). Stratification by initial FEV_1% predicted demonstrated a significantly decreased decline in FEV_1 in individuals with moderate airflow obstruction (i.e., FEV_1 of 31 to 65% predicted). The results of the current Registry, although observational, are consistent with the observation of a slowing in the decline of FEV_1 in augmentation-therapy recipients with moderate airflow obstruction, but extend this observation. Features of the current study include measurement of

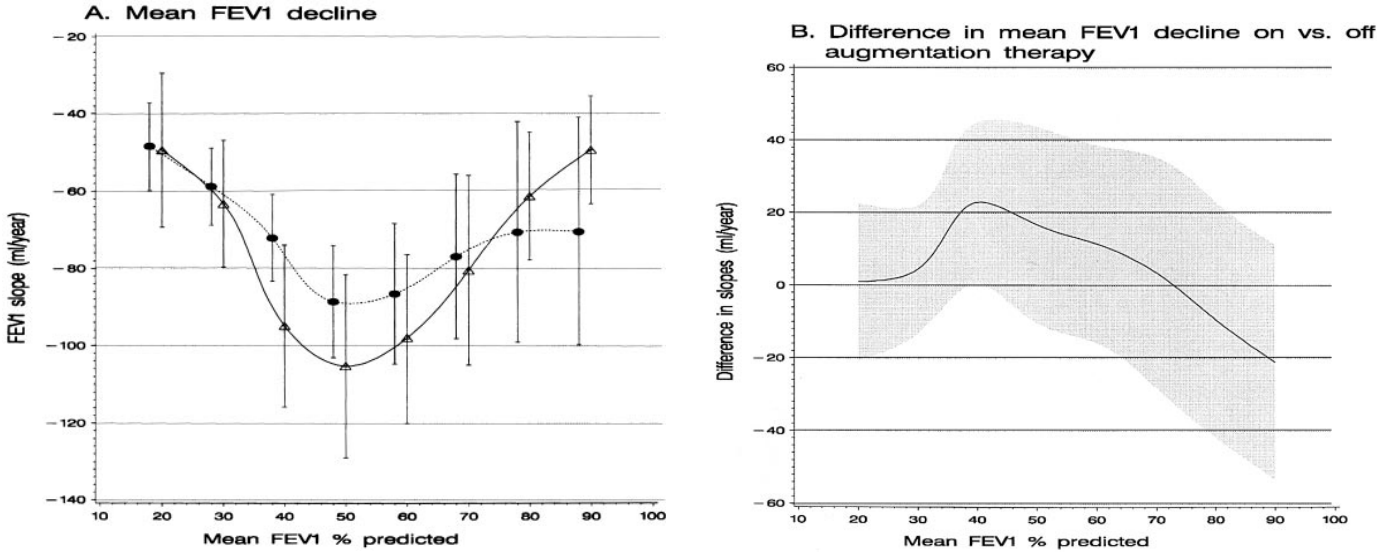

Figure 3. Mean FEV_1 decline by level of FEV_1% predicted and augmentation-therapy status. (*A*) Estimated mean decline in FEV_1 (ml/yr), with 95% confidence limits, as a function of mean FEV_1% predicted, for subjects receiving augmentation therapy (*solid dot*, *dashed line*) and those not receiving augmentation therapy (*triangle*, *solid line*). These estimates were obtained by fitting a multivariate mixed-effects model relating FEV_1 change from baseline to cumulative time receiving and not receiving augmentation therapy, with the model adjusted for age, mean FEV_1, gender, smoking status, and augmentation therapy, and including an interaction between use of augmentation therapy and mean FEV_1% predicted. Nonlinear effects of age and mean FEV_1 were modeled with cubic spline regression methods, with knotpoints for mean FEV_1 at 20%, 35%, 50%, 65%, and 80% predicted, and knotpoints for age at 30, 35, 45, 55, and 65 yr. These are "least-squares" means, which average over the other factors (i.e., age, gender, and smoking status). (*B*) Estimated difference in mean rates of FEV_1 decline with and without augmentation therapy. Differences in the means shown in *A* are plotted against mean FEV_1% predicted, with 95% CIs indicated by the *shaded region*. A positive difference in slopes implies that the rate of decline in FEV_1 is less negative for subjects receiving versus those not receiving augmentation therapy.

survival as a primary outcome, extensive attention to quality control of spirometric measurements, assurance that all FEV_1 measurements were postbronchodilator values and statistical modeling to consider the impact of concurrent therapies (e.g., supplemental oxygen).

Furthermore, although the lack of trough serum levels of α_1-AT in augmentation-therapy recipients precluded assurance that values exceeded the "protective level" target value of 11 μM throughout the dosing interval, available studies of intravenous augmentation therapy suggest that protective levels are exceeded for at least most of the dosing interval with weekly, biweekly, and monthly therapy (5–7, 37).

Our finding that recipients of augmentation therapy have better survival than do nonrecipients, and that the rate in decline of FEV_1 was slowed in recipients with FEV_1 values of 35 to 49% predicted suggests the clinical efficacy of augmentation therapy, although these differences may have been due to factors for which we could not control. A definitive conclusion will require a randomized controlled trial.

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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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