Mortality in Individuals With Severe Deficiency of α1-Antitrypsin*

Findings From the National Heart, Lung, and Blood Institute Registry

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Study objective: **To clarify the mortality rate and causes of death of individuals with α_1-antitrypsin (AAT) deficiency, the Death Review Committee (DRC) of the National Heart, Lung, and Blood Institute Registry of Individuals with Severe AAT Deficiency reviewed all available medical records regarding the deaths of study subjects during Registry follow-up (up to 7.2 years).**
Methods: **Individual determinations by each member of the three-person DRC led to consensus judgments regarding the underlying cause and the immediate and contributing causes of death.**
Results: **Of the 1,129 Registry subjects, 204 died (18.1%) [approximately 3%/yr]. Record availability permitted detailed review in 120 decedents, and death certificates were available in 56 of the remaining 84 subjects (67%). Emphysema and cirrhosis were the most common underlying causes of death (72% and 10%, respectively), with malignancy and diverticulitis accounting for 3% of deaths each. To assess attributable mortality, standardized mortality ratio analysis was performed and indicated that excess mortality was ascribable entirely to lung and liver disease.**
Conclusions: **We conclude that severe AAT deficiency poses a significant threat to health, that severe airflow obstruction is a major determinant of mortality, and that liver and lung disease account for the excess mortality in affected individuals. These findings support current efforts to enhance diagnostic recognition and treatment of AAT-deficient individuals.**
(CHEST 2005; 127:1196–1204)

Key words: α_1-antitrypsin deficiency; cause of death; mortality; registry; standardized mortality ratio

Abbreviations: AAT = α_1-antitrypsin; CI = confidence interval; DRC = Death Review Committee; NHLBI = National Heart, Lung, and Blood Institute; SMR = standardized mortality ratio

Severe deficiency of α_1-antitrypsin (AAT) confers risk of early onset emphysema and, in the case of AAT-deficient variants with the Z or several other alleles, the risk of liver disease.[1,2] To address gaps in existing knowledge about the natural history of AAT deficiency, the National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT was launched in 1989 and conducted a long-term follow-up of the largest available cohort of severely AAT-deficient individuals

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Dr. Stoller has served as a scientific advisor for Baxter and Bayer.
This research was conducted with the support of the National Heart, Lung, and Blood Institute of the National Institutes of Health, contract NO1-HR-86036.
Manuscript received April 12, 2004; revision accepted September 7, 2004.

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(n = 1,129) at 37 participating clinical centers throughout North America.[3,4] To date, the Registry has provided insights into the clinical features of affected individuals, the rate of progression of obstructive lung disease, the efficacy of IV augmentation therapy, and adverse experiences and patterns of prescribing augmentation therapy.[3–6]

As part of the activities of the Data Coordinating Center in the Registry, a Death Review Committee (DRC) reviewed all available records on individuals who died over the course of Registry follow-up in order to determine the specific causes of death. The current report extends available findings from the Registry by presenting the results of the DRC analysis regarding the mortality rate and the specific causes of death for these decedents.

Materials and Methods

As described previously,[3–5] eligibility criteria for Registry enrollment included the following: age ≥ 18 years; severe AAT deficiency, defined as a serum level < 11 μmol/L (as confirmed by the Central Phenotype Laboratory of the Registry); and written informed consent. Altogether, 1,129 eligible participants enrolled between March 1989 and October 31, 1992. Registry participants were followed up for a mean of 4.4 years (range, 0 [for subjects who died before the first follow-up visit at 6 to 12 months] to 7.2 years).

Participant deaths were ascertained in reports from the 37 clinical centers (where follow-up visits were conducted every 6 to 12 months throughout the Registry) or by inquiries to death review services, the National Death Index (National Center for Health Statistics, Hyattsville, MD) and Equifax (McLean, VA). For each death, medical records were sought that would best describe the events surrounding the death; these records included medical charts from the terminal hospitalization, final outpatient visits (especially if the subject died at home), and the death certificate. Importantly, determinations of the cause of death reported in this series were based on independent review of records and not causes stated on the death certificate.

Using these available records, the cause of each subject's death was determined by a DRC comprised by three of the study investigators (H.P.W. [Chair], J.K.S., and J.T.). Definitions of causes of death were decided *a priori*, were distributed to each DRC member, and were based on coding definitions for death certificate completion. Specifically, for each evaluable decedent, the DRC was asked to determine the following: (1) a single underlying cause of death (defined as "the single disease or injury that influenced the events resulting in death"); (2) a single immediate cause of death (defined as the "single final disease, injury, or complication directly causing the death"); (3) other causes deemed contributing to death; (4) all conditions being present but not contributing to death; and (5) whether or not the death was deemed attributable to a complication of augmentation therapy.

To assign the cause of death, each DRC member independently reviewed all available records and assigned the aforementioned death-related categories. Consensus ratings by the three DRC members were achieved in a series of face-to-face meetings, and consensus ratings were used for all analyses in this study.

Reports of postmortem examinations were available for 58 decedents. In another 126 decedents, postmortem examinations were known not to have been performed, and postmortem examination status was uncertain in 20 decedents. Pathology findings in these postmortem examinations are the subject of a separate report.[7]

Statistical Analysis

Univariate comparisons of two groups were made using the two-sample *t* test for continuous outcomes and the χ^2 test for categorical outcomes. Cumulative mortality curves since enrollment in the Registry were estimated using the Kaplan-Meier method using data from all 1,129 subjects in the Registry in which surviving patients were censored at the time of last Registry contact. Survival curves were compared using the log-rank test. The Cox proportional hazards model was used to examine the independent effects of baseline and time-varying predictors on survival. In this model, baseline factors examined included gender, education, age, and level of postbronchodilator FEV_1 percentage of predicted at enrollment. Lung transplant status and whether the subject was currently receiving IV augmentation therapy were treated as binary, time-varying covariates. Following our previously reported approach,[5] when fitting the Cox regression models, we used a landmark analysis approach in which only patients who had been contacted ≥ 6 since enrollment (1,048 subjects, 147 deaths) were included. This approach reduced the possibly biasing effects of those patients who were very ill when enrolled and who died before they could begin augmentation therapy or return for an additional follow-up visit. Because we previously reported on the relationship of augmentation therapy to survival using a more detailed analysis and model,[5] we do report risk ratios for augmentation therapy in this article. To compare death rates in the Registry to the general population, standardized mortality ratios (SMRs) were computed as the ratio of observed to expected deaths, in which expected numbers of deaths were obtained using age/gender-specific death rates published in the 1992 Statistical Abstract of the United States,[8] which was concurrent with the Registry. Confidence intervals for SMRs were computed from the exact Poisson distribution.[9]

Results

Of the 1,129 Registry enrollees, 204 subjects (18.1%) died over the course of follow-up, at a relatively linear rate of approximately 3%/yr (Fig 1). Univariate comparison of baseline features of 204 decedents with those of the 925 survivors (Table 1) showed that subjects who died over the course of Registry follow-up were older (51 ± 11 years vs 45 ± 10 years, $p < 0.0001$) [mean ± SD], had a slightly higher serum AAT level (6.2 ± 1.3 μmol/L vs 5.7 ± 1.4 μmol/L, $p < 0.0001$), had a lower postbronchodilator FEV_1 percentage of predicted (29.4 ± 18.8% vs 50.5 ± 30.4%, $p < 0.0001$), were more frequently ex-smokers or current smokers ($p = 0.02$), and had a lower educational level ($p < 0.0001$). Also, receipt of any kind of a transplant or of a lung transplant was more common among decedents than survivors ($p < 0.0001$ for both comparisons).

As an example of the longitudinal effect of base-