



Survival Improvements in Alpha-1 Antitrypsin Deficiency



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Abstract

RATIONALE: Alpha-1 antitrypsin deficiency (AATD) is a single gene mutation that leads to decreased levels of alpha-1 antitrypsin protein in the blood and an increased risk of lung and liver disease. The precocious onset and severity of disease in AATD has been assumed to lead to early mortality in individuals. In 1994, Seersholm and colleagues (Thorax 1994;94:695) presented survival data on 565 individuals in the Danish AATD registry. They found the overall median survival of individuals with AATD to be 54.5 years and this number has been widely cited ever since. With much larger numbers of individuals with AATD available at present as well as changes in management, it is important to reevaluate survival in those with AATD. **METHODS:** AlphaNet is a not-for-profit disease management organization that has followed over 3,000 individuals with AATD since 1999. 91% of those followed by AlphaNet have lung disease and most of these are receiving intravenous augmentation therapy as well as AlphaNet's formal disease management program. We reviewed the mortality data from 2,365 individuals followed by AlphaNet since an electronic health record was established and evaluated survival using SAS Lifetest modified Kaplan-Meier procedure including analysis for influence of smoking and sex. **RESULTS:** The overall median survival in the AlphaNet population was 60.3 years (95% C.I.: 59.6-60.8). Unlike the Seersholm paper, we found a significant influence of smoking, with non-smokers having a median survival of 65.5 years and smokers of 58.8 (p<.0001). **CONCLUSION:** The results obtained in the AlphaNet population suggest a better survival than that previously reported even though this population is highly enriched for those with significant lung disease. There are many potential explanations including the differences between the study populations, the extensive use of augmentation therapy in this U.S. population, the well-documented effectiveness of AlphaNet's disease management program. Regardless of the explanation, this is good news for those treating AATD and especially for those diagnosed with AATD.

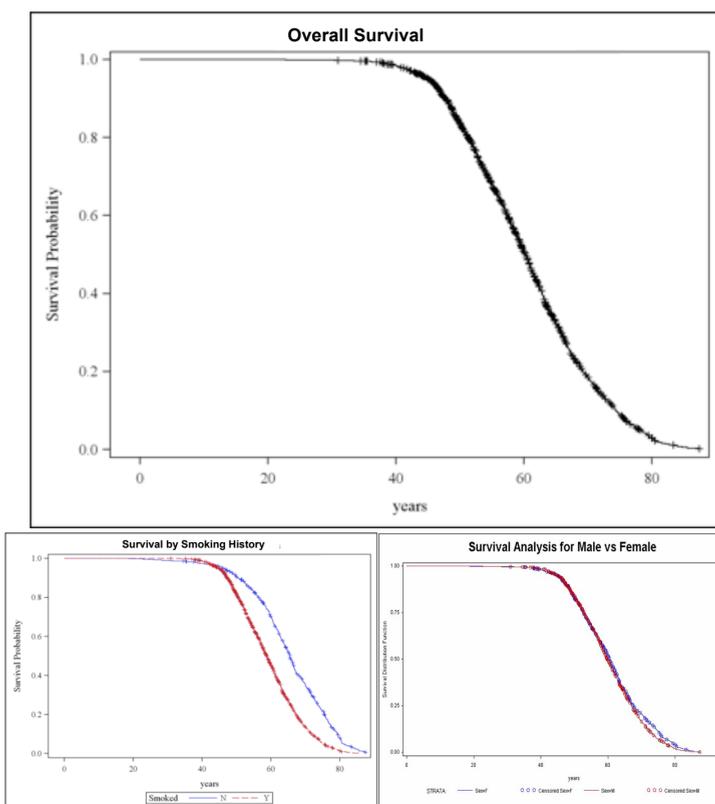
Background

- AlphaNet is a not-for-profit, health maintenance organization that has served over 3,000 patients in the U.S. with alpha-1 antitrypsin deficiency (AATD) since its founding in 1995
- Nearly all those who enroll in AlphaNet are receiving augmentation therapy for lung disease related to Alpha-1
- We have collected mortality data on enrollees for over a decade and also collect quality of life, healthcare utilization, employment, insurance, and other data
- Most publications regarding the survival of patients with AATD reference a single Danish publication (Thorax 1994;94:695) from Seersholm et al. which calculated the following survival numbers based on the evaluation of 397 individuals with severe AATD:
 - **54.5 years** for all evaluated subjects
 - **49.4 years** for index cases (n=252)
 - no difference between smokers and non-smokers or males and females

Methods

We reviewed the mortality data from 2,365 individuals followed by AlphaNet since an electronic health record was established. All had severe AATD and were on augmentation therapy for lung disease. We evaluated survival using SAS Lifetest modified Kaplan-Meier procedure including analysis for influence of smoking and sex. Non-smokers were defined as smoking less than 1 pack of cigarettes throughout their lives.

Results



Results (cont)

- The overall mortality (median survival) of the AlphaNet population between 1999 and 2010 was **60.3 years** (95% C.I.: 59.6-60.8). Virtually all these subjects would be considered index cases.
- We found a significant effect of smoking on survival with non-smokers having a median survival of **65.5 years** and smokers of **58.8 years** (p<.0001).
- We found no survival difference between men and women.

Discussion

This study evaluated the survival of individuals with AATD followed by a health maintenance program. The data suggest that survival in AATD has improved dramatically over the past decade (from 49.4 years to 60.3 years or to 65.5 years for non-smoking AATD patients) compared with data reported from Denmark in the early 1990s. This study does not provide an explanation for this survival improvement.

While Seersholm et al. used the method of cumulative survival probabilities estimated by the life table method and we we relied on a modified Kaplan-Meier procedure, these should provide comparable results. The fact that Seersholm found no difference between smokers and non smokers may be explained by the very small number of non-smokers in his cohort and his more liberal definition of non-smoker.

Possible explanations for the improved survival include our evaluation of individuals on augmentation therapy; the success ADMAPP health maintenance program of AlphaNet, which has been shown to improve quality of life, exacerbation frequency, and healthcare utilization of individuals with AATD; or perhaps better overall understanding of AATD among treating physicians.

Conclusions

- Survival for individuals with alpha-1 antitrypsin deficiency and lung disease appears to have improved dramatically, although the exact explanation for that improvement is currently unknown
- This study evaluated a different, much larger population of index cases with lung disease than previous publications and all were on augmentation therapy. This survival data is quite encouraging for patients with AATD and for the healthcare providers who care for them

Questions

- What has led to the survival improvements noted in this study?
- Can further improvements be made?
- What is the effect of augmentation therapy on survival, since subjects included in this study were receiving augmentation?
- Can a patient-directed self-management program such as AlphaNet's actually affect survival?