Mortality in alpha-1-antitrypsin deficiency in the United Kingdom

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Received 20 September 2008; accepted 5 April 2009
Available online 13 May 2009

KEYWORDS
Alpha-1-antitrypsin deficiency; Cause of death; Computerised tomography; Lung function; Mortality; Registry

Summary
Background: Four hundred and eighty-eight PiZ alpha-1-antitrypsin deficient patients, who had joined the UK registry over a 9-year period, were followed in an observational study to determine mortality. None had received A1AT augmentation therapy.

Methods: Cause of death was confirmed from death certification and medical records. Patients were censored according to length of time on the program or until they withdrew from the program.

Results: There were 56 deaths of which 30 were attributed to respiratory causes. Of the remaining 26 deaths, 4 were due to complications from lung transplant, 6 due to liver disease (including 2 post-liver transplant) and the other 16 due to a variety of causes. Kaplan–Meier plots indicated a cumulative hazard for mortality of 18.1% in 9 years, correcting for time of follow up. When categorised for FEV1 percent-predicted, the group with severe impairment had increased mortality \( p < 0.001 \) compared with the mild group and there was a direct relationship between severity and mortality. The severe group had increased mortality compared with the mild group when categorised for KCO percent-predicted \( p < 0.001 \), RV/TLC ratio \( p < 0.001 \) or emphysema score on CT scan \( p < 0.001 \) upper zone). Cox regression analyses indicated that these relationships remained when corrected for age. There were no differences in mortality after categorisation for educational level or occupational group.

Conclusion: Mortality in a cohort of A1AT deficient patients (PiZ phenotype) in the UK was 2% per year and was associated with lung function impairment and emphysema severity on CT scan, but not social status.

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Introduction

Alpha-1-antitrypsin deficiency (A1ATD) is classically associated with early onset rapidly progressive emphysema. The prognosis has been considered to be poor with early mortality in identified cases. Recent data from the
American A1ATD register described an overall mortality of around 3% per year. The majority of deaths (72%) were due to emphysema and around 10% were related to liver cirrhosis. A previous study from the same database showed that lower forced expiratory volume in 1 s (FEV1), higher age, lower educational level, and lung transplant were the major predictors of mortality. Although FEV1 has been considered the gold standard for the prediction of mortality in the context of usual chronic obstructive pulmonary disease (COPD), our own studies have indicated that the best predictors of mortality in A1ATD are measures of the severity of emphysema, namely carbon monoxide gas transfer corrected for lung volume (KCO) and especially lung densitometry on computerised tomography (CT) scan.

Augmentation therapy is widely available in the USA and it is generally believed that replenishment of alpha-1-antitrypsin (A1AT) in deficient subjects should decrease the progression of emphysema. Indeed comparisons between subjects receiving and not receiving augmentation therapy have suggested that lung function decline is greatest in those with no therapy. Furthermore data also suggested that mortality was seen to be decreased in subjects receiving augmentation therapy, particularly in those with an FEV1 predicted of 35–49%. Although these data are consistent with a beneficial effect of augmentation therapy on lung function decline, several confounding factors may have influenced the mortality data including socioeconomic factors that would influence the affordability of augmentation as well as general health. In addition, those receiving augmentation therapy would by necessity have regular exposure to health care facilities, which in itself may have a beneficial effect.

Although we had published previous information on overall mortality in 256 patients for over 4 years, we took the opportunity to describe subsequent mortality and survival experience in the UK ADAPT (Antitrypsin Deficiency Assessment and Programme for Treatment) programme for over 9 years. We explored factors that determined mortality and survival, which included information on social status. Unlike the patients on the US registry, none of the A1ATD patients on our programme had ever received augmentation therapy, but they all had universal and free access to health care facilities.

**Methods**

The ADAPT programme assesses A1ATD patients annually in a single centre. Patients undergo lung function testing according to the Association of Respiratory Technology and Physiology (ARTP)/British Thoracic Society (BTS) guidelines including the measurement of post-bronchodilator (400 µg salbutamol) flow rates and carbon monoxide uptake as a measure of gas transfer using the single breath method. The results are expressed as a percentage predicted value for the patient’s age, sex and height. The equipment used was MasterScreen PFT (Jaeger, Germany) and quality control of equipment and technicians was according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) standards. Patients also have CT scans for quantitative lung densitometry.

High resolution computerised tomography (HRCT) scans were performed using a GE Pro speed Scanner (General Electric Medical Systems, Milwaukee, USA) to obtain 1 mm slices. The scanner was calibrated weekly for water and air. A full scan was performed at maximal inspiration (10 mm intervals) and a limited scan on expiration (30 mm intervals). Two slices were chosen for analysis: the level of the aortic arch (upper zone) and the level of the inferior pulmonary vein/right atrial confluence (lower zone). The data were subjected to density mask analysis, which highlighted lung voxels with a density less than −910 Hounsfield Units (HU). The Voxel Index is the percentage of highlighted voxels with a lower density than this arbitrarily chosen threshold, reflecting the proportion of emphysematous tissue.

A cohort of the first 488 patients with A1ATD, Protease Inhibitor Z (PIZ) phenotype, who joined the ADAPT program in Birmingham, UK, over the 9-year period from July 1996 to July 2005 were studied. None received A1AT augmentation since it is not licensed for use in the UK.

Causes of death were ascertained from death certification, hospital medical records and by contacting the family practitioners. Deaths primarily related to emphysema, or an exacerbation of COPD including bronchial infection or pneumonia leading to respiratory failure, were classified as respiratory. For the purposes of this study deaths due to pulmonary embolus were classified as non-respiratory, as were post-lung-transplant deaths because they were not directly related to the original emphysema.

Data were collected prospectively as part of a wider project to study the natural history of progression of the disease in A1ATD. Since the patients had joined the program at different times over the 9 years, they were censored (i.e. removed from the analysis) according to the length of time they had been on the program, or until they withdrew from the program (72 cases). In the Kaplan–Meier analyses, by design, the patients were censored on the date they left the programme and the mortality rate would not be affected by their withdrawal, with the assumption that the patients who withdrew were no more or less likely to die than those who remained in the analysis. Kaplan–Meier plots were made for all-cause mortality. Categorisation analysis involved splitting these plots into severity groups in order to perform statistical comparisons. The original Kaplan–Meier plots were categorised into 4 severity groups according to the lung function, as determined by the FEV1, KCO and RV/TLC ratio, and CT Voxel Index (1 = mild, 2 = mild–moderate, 3 = moderate–severe, 4 = severe). FEV1 was divided according to the GOLD (Global initiative for chronic Obstructive Lung Disease) criteria, but the other measures were divided arbitrarily to provide broadly equal numbers in order to obtain a reasonable spread of patients across groups. The Kaplan–Meier plots were also categorised for occupational and educational status, using information from baseline patient questionnaires. The three educational groups were determined according to the length of continued education: (1) university or professional level (finishing age 21 or older), (2) further education level (finishing age 18 or older), and (3) high school or secondary education only (finishing age 16 or younger if the subject left school). The three occupational groups were determined according to the type of employment based on
social class categories: (1) professional, managerial or technical (Social Class I or II), (2) skilled non-manual or manual (Social Class IIIa or IIb), (3) partly skilled, unskilled or long-term unemployed (Social Class IV or V). Finally the Kaplan–Meier curves were categorised for 4 age groups. A Cox regression analysis of each parameter against mortality was performed, correcting for age.

Ethical approval was granted by the local research and ethics committee and all patients gave informed consent for the investigations.

Analysis

Survival curves were plotted using Kaplan–Meier analysis (SPSS® version 12.0). Categorisation for FEV1, KCO, RV/TLC and education and occupation was performed within this analysis. Statistical comparison between groups was performed using Tarone–Ware pairwise analysis (SPSS® version 12.0). A p-value of <0.05 was taken as statistically significant. Cox regression analyses were performed for each parameter in order to correct for age (SPSS® version 12.0).

Results

Baseline characteristics of the 488 patients included in the analysis are illustrated in Table 1. There were 56 deaths in total in this cohort of patients over the 9-year period. Median length of follow up was 4.31 years and mean was 8.68 years. Causes of death are illustrated in the pie chart in Fig. 1. The majority of deaths were secondary to underlying emphysema (30 out of 56, 43.1%). Five died of various malignancies (8.9% compared with 3% from the US registry). Five died of various malignancies (8.9% compared with 3% from the US registry); one each of lung, oesophagus, lymphoma, stomach and brain tumours. The remainder of the deaths consisted of a miscellaneous group including cerebrovascular, cardiac, thromboembolic and other causes including pancreatitis, pulmonary haemorrhage and after lung volume reduction surgery.

There had been 72 withdrawals from the program out of the 488 patients. Of these, 39 were confirmed to be still alive when contacted by mail, 3 were confirmed as dead and 30 did not reply or were no longer known at the address in our database. However, since each patient was censored at the time of withdrawal from the program (reducing the denominator in Kaplan–Meier analysis by 1), this would not affect the results of the analysis assuming those who withdrew were no more or less likely to die than those who remained. Those who withdrew did have a slightly lower average baseline FEV1 than those who remained (49.72% predicted [standard error 3.22%] versus 57.02% [standard error 1.57%], respectively), although this was not statistically significant. The data for these withdrawals are summarised in Table 2.

Kaplan–Meier analysis shows a cumulative mortality of 18.1% over the 9-year period. Fig. 2a shows the survival curves categorised for FEV1 percent-predicted, divided into 4 severity groups: >>80%, 50–79%, 30–49% and <30%. The data confirm the stepwise relationship of mortality to the severity of the airflow obstruction. Fig. 2b shows the survival curves categorised for KCO, divided into 4 severity groups: >80% predicted, 60–79% predicted, 40–59% predicted and <40% predicted. The data demonstrate little relationship between KCO and mortality except for the most severely affected group (<40% predicted), which shows a significantly increased mortality compared with the other groups. Fig. 2c illustrates a significant relationship between worse survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Whole group (n = 488)</th>
<th>Survivor (n = 432)</th>
<th>Non-survivor (n = 56)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.00 (0.48)</td>
<td>49.40 (0.51)</td>
<td>54.70 (1.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>60.70</td>
<td>58.90</td>
<td>74.50</td>
<td>0.025</td>
</tr>
<tr>
<td>Assessment length (years)</td>
<td>4.45 (0.10)</td>
<td>4.65 (0.10)</td>
<td>2.85 (0.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>55.99 (1.40)</td>
<td>58.20 (1.51)</td>
<td>39.51 (3.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KCO (%predicted)</td>
<td>68.61 (1.09)</td>
<td>69.83 (1.13)</td>
<td>59.37 (3.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>CT scan Voxel Index (upper zone, inspiratory)</td>
<td>31.26 (0.79)</td>
<td>30.02 (0.82)</td>
<td>41.03 (2.15)</td>
<td>&gt;0.0001</td>
</tr>
<tr>
<td>CT scan Voxel Index (lower zone, inspiratory)</td>
<td>44.36 (0.93)</td>
<td>43.20 (0.98)</td>
<td>53.48 (2.51)</td>
<td>0.002</td>
</tr>
<tr>
<td>Incidence of emphysema (%)</td>
<td>78.70</td>
<td>77.00</td>
<td>91.80</td>
<td>0.017</td>
</tr>
<tr>
<td>Incidence of chronic bronchitis (%)</td>
<td>39.80</td>
<td>39.50</td>
<td>41.80</td>
<td>ns (0.740)</td>
</tr>
<tr>
<td>Incidence of reversibility to bronchodilators</td>
<td>55.50</td>
<td>55.90</td>
<td>52.70</td>
<td>ns (0.659)</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>67.0</td>
<td>66.7</td>
<td>69.1</td>
<td>ns (0.654)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>10.5</td>
<td>10.2</td>
<td>12.7</td>
<td>ns (0.631)</td>
</tr>
<tr>
<td>Pack years</td>
<td>16.43 (0.66)</td>
<td>16.32 (0.70)</td>
<td>17.26 (1.99)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Index cases (%)</td>
<td>88.60</td>
<td>87.00</td>
<td>100</td>
<td>0.009</td>
</tr>
</tbody>
</table>

For quantitative data means are shown with standard errors in brackets. For frequency data, percentages are shown. All statistics on quantitative variables used Mann–Whitney U test because of non-normal distributions, except age which is normally distributed throughout so t-test was used. Frequencies were tested using Chi-squared test. Significance shown for differences between survivors and non-survivors. Abbreviation: FEV1 = forced expiratory volume in 1 s; KCO = gas transfer corrected for alveolar volume; RV = residual volume (L); TLC = total lung capacity (L); CT = computerised tomography; ns = not significant. Chronic bronchitis was defined as daily production of sputum for at least 3 months of at least 2 consecutive years.
and gas trapping, expressed as residual volume (RV) divided by total lung capacity (TLC). Fig. 3 shows the survival curves for extent of emphysema on CT lung densitometry for upper zone CT scans. Results were similar for lower zone scans (data not shown). The data indicate a relationship of higher Voxel Index (signifying worse emphysema) to worse mortality. Survival curves categorised for educational level and occupational status indicated no effect on mortality.

There is a significant effect of age on mortality as expected (Fig. 4). However, when Cox regression analyses were performed for each parameter against mortality with correction for age, the relationship of mortality to each parameter remained strong. This is illustrated in Table 3 which compares the hazard ratio for mortality comparing the two extreme categorisation groups for each parameter, with and without correction for age. After age correction the hazard ratios are slightly reduced, which is reflected as minor changes in the p-values although the relationship of the parameter to mortality is retained.

Discussion

This observational mortality study has outlined the mortality rate and causes of death in A1AT deficient subjects in the UK, and has described the associations of mortality with lung function measurements and CT scan emphysema scores. It is unique in that it includes a large cohort of A1ATD patients studied over a 9-year period, none of whom had access to or had received A1AT augmentation therapy, but all of whom had free access to health care facilities.

Few studies of overall mortality have been reported in A1ATD. The original studies by Larsson22 noted that life expectancy was reduced in Swedish subjects compared with the general population. This reduction was greater in smokers and males compared with non-smokers and females. A more recent report from the Swedish registry of non-smoking PiZ individuals has shown a standardised mortality ratio of 2.32 compared with the general population, but no increased mortality risk in the individuals was identified by screening.23

Subsequent mortality rates have been described from the National Institutes of Health (NIH) registry in the USA. The original publication in 19982 indicated that there was a difference between subjects who had ever received augmentation compared with those who had never received such therapy. Over a mean 57-month period of follow up the adjusted relative risk of death was 0.64 (0.43–0.94) in the 68.9% of patients who had received augmentation therapy. Whereas this suggested a benefit of augmentation therapy it was recognised that differences in educational and social status, which would affect access to the health care system, may have influenced the outcome. The overall

Table 2  Comparative data on patients who withdrew from the study programme and those who remained.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Withdrawn</th>
<th>Not withdrawn</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.10 (1.21)</td>
<td>50.48 (0.52)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gender (%male)</td>
<td>56.30</td>
<td>61.10</td>
<td>ns (0.52)</td>
</tr>
<tr>
<td>Assessment length (years)</td>
<td>5.19 (0.25)</td>
<td>4.32 (0.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>49.72 (3.22)</td>
<td>57.02 (1.57)</td>
<td>ns (0.12)</td>
</tr>
<tr>
<td>KCO (%predicted)</td>
<td>66.90 (3.04)</td>
<td>68.89 (1.20)</td>
<td>ns (0.38)</td>
</tr>
<tr>
<td>CT scan Voxel Index (upper zone, inspiratory)</td>
<td>30.28 (2.71)</td>
<td>31.41 (0.98)</td>
<td>ns (0.57)</td>
</tr>
<tr>
<td>CT scan Voxel Index (lower zone, inspiratory)</td>
<td>45.04 (3.21)</td>
<td>44.25 (1.15)</td>
<td>ns (0.68)</td>
</tr>
<tr>
<td>Incidence of emphysema (%)</td>
<td>75.0</td>
<td>79.3</td>
<td>ns (0.44)</td>
</tr>
<tr>
<td>Incidence of chronic bronchitis (%)</td>
<td>44.3</td>
<td>39.0</td>
<td>ns (0.40)</td>
</tr>
<tr>
<td>Incidence of reversibility to bronchodilators</td>
<td>66.2</td>
<td>52.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>64.3</td>
<td>67.5</td>
<td>ns (0.39)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>17.1</td>
<td>9.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Pack years</td>
<td>16.64 (1.61)</td>
<td>16.40 (0.72)</td>
<td>ns (0.71)</td>
</tr>
<tr>
<td>Index cases (%)</td>
<td>88.5</td>
<td>88.4</td>
<td>ns (0.98)</td>
</tr>
</tbody>
</table>

For quantitative data means are shown with standard errors in brackets. For frequency data, percentages are shown. All statistics on quantitative variables used Mann–Whitney U test because of non-normal distributions, except age which is normally distributed throughout so t-test was used. Frequencies were tested using Chi-squared test. Significance shown for differences between patients withdrawn and not withdrawn. Abbreviation: FEV1 = forced expiratory volume in 1 s; KCO = gas transfer corrected for alveolar volume; RV = residual volume (L); TLC = total lung capacity (L); CT = computerised tomography; ns = not significant. Chronic bronchitis was defined as daily production of sputum for at least 3 months of at least 2 consecutive years.
mortality of 18.1% in 9 years for patients not on A1AT therapy reported in the present study is lower than in the second study from the NIH registry published more recently. The latter reported a mortality rate of around 3% per year, although it is not stated what proportion of the patients received A1AT augmentation. However, the similarity of the mortality rate to that of subjects on augmentation therapy reported in the earlier NIH report suggests that the majority were on therapy, since the mortality rate for US subjects who ever received augmentation in that study was 3.1% per year (106 deaths in 722 subjects) over the average 57 months of follow up, compared with 2.6% in those who were never on therapy. Although the mortality rate for UK patients is similar to that seen for US patients on augmentation therapy it does not necessarily negate an effect of this therapy on mortality. The two populations

Figure 2 (a) Kaplan–Meier survival curve categorised for FEV₁ (n = 472, 56 deaths). Group 1 = ≥80% predicted (n = 102, 3 deaths). Group 2 = 50–80% predicted (n = 121, 8 deaths). Group 3 = 30–50% predicted (n = 149, 22 deaths). Group 4 = <30% predicted (n = 100, 23 deaths). Significant differences between groups are shown. (b) Kaplan–Meier survival curve categorised for KCO (n = 462, 54 deaths). Group 1 = ≥70% predicted (n = 135, 10 deaths). Group 2 = 50–70% predicted (n = 157, 17 deaths). Group 3 = 30–50% predicted (n = 124, 14 deaths). Group 4 = <30% predicted (n = 46, 13 deaths). Comparisons of Groups 1–3 are not statistically significant; differences with Group 4 are shown. (c) Kaplan–Meier survival curve categorised for RV/TLC (n = 465, 50 deaths). Group 1 = RV/TLC < 30% (n = 114, 5 deaths). Group 2 = RV/TLC 30–40% (n = 169, 10 deaths). Group 3 = RV/TLC 40–50% (n = 123, 20 deaths). Group 4 = RV/TLC ≥ 50% (n = 59, 15 deaths). Significant differences between groups are shown.
Group 3 has a lower mortality than Group 2, but the 2 groups
Significant differences between groups are shown. In this graph
45% (n = 140, 13 deaths). Group 3 = 50–60 predicted
30% (n = 168, 18 deaths). Group 4 = ≥60 (n = 86, 19
differences between groups are shown.
194) in usual COPD.24 In
By the previous finding that basal emphysema affects FEV1
is an effect on mortality. An alternative view is supported
equivalent analysis from the US registry is available.
us is likely to reflect the socialised model of health care
in the UK, where it is possible that even though a much
lower percentage of the country’s gross domestic product is
spent on health than in the USA, there is a more equitable
distribution of resources across socioeconomic groups. This
also supported by our data categorised for occupational
groupings on the definitions of social class, although
cannot be independently verify the cause of death in
many cases, since there is no central registry of death.
However, it can be assumed that the records of family
practitioners are accurate since either they have
completed the death certificate themselves if the patient
died outside of hospital, or they have been in receipt of
certification and records of family practitioners. Since
patients visited the centre from all over the country, it was
impossible to independently verify the cause of death in
the hospital in which the patient died. The major causes of death (30 out of 56,
53.6%) relate directly to emphysema. If deaths related to
lung transplant were counted as respiratory deaths this
would be 60.7%, still lower than that reported due to
emphysema in the NIH registry.\textsuperscript{1} This is in contrast to a recent study of mortality in usual COPD\textsuperscript{27} where only 35\% of the deaths were "respiratory" (excluding lung cancer). However, this latter study showed a much higher proportion of cardiovascular deaths (27\%) than our A1ATD patients (5.4\%), probably reflecting the younger age group and hence lack of comorbidity in our patients for equivalent severity of COPD. In addition there was also a lower pack year history in the especially susceptible patients in the present study, despite similar impairment in FEV\textsubscript{1}, which may also have had an effect on comorbidities.

Some limitations in this study have been discussed. Comparisons with patients in the US are limited by the different case mix of patients between the A1AT deficiency registries of the two countries, the UK patients on average having milder disease as measured by FEV\textsubscript{1}. Also there are so many variables in 2 quite different health care systems that it is difficult to identify potentially important aspects that may affect mortality. The Kaplan–Meier analyses correct for patients withdrawing from follow up by censoring at the time they leave, it is possible that some patients who withdrew had more physiological impairment (though not significantly different as a group) than those who remained, which could influence mortality. Thirty of the withdrawals could not be traced and the assumption had to be made that these had the same likelihood of survival as the other subjects in the study. Finally, there could be possible biases in the recording of death certification data, since most deaths occurred outside our institution so medical notes could not always be verified independently. However, although this could influence the cause of death it would not alter the overall mortality rate.

In summary we have found that mortality in UK of A1ATD patients is 18.1\% over 9 years (2\% per year). This is influenced by the baseline FEV\textsubscript{1}, RV/TLC, KCO and the extent of emphysema on CT scan, but not social class or educational level. The mortality rate is similar to that seen in the USA for patients on augmentation therapy, however differences in the populations studied in the two countries indicate that the results of randomised controlled trials of this treatment on mortality will be necessary to determine the true effect.

Conflicts of interest

RAS has received non-commercial research funding from Talecris/Bayer Biologicals towards the UK database used for the submitted publication. In addition he has acted in an advisory role to Baxter, Kamada and Aventis Behring all of whom have AAT available as a therapeutic product. RAS has lectured at scientific meetings on all aspects of AAT deficiency including several symposia funded by Talecris/Bayer Biologicals. None of the other authors have competing interests to declare.

Acknowledgements

The ADAPT programme is funded by Talecris Biotherapeutics.

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