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Rate of progression of lung function impairment in α_1-antitrypsin deficiency

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ABSTRACT: The aim of the present study was to identify α_1-antitrypsin (α_1-AT)-deficient patients who had rapidly progressive disease.

PiZ patients (n=101) underwent annual lung function measurements over a 3-yr period, and the results were related to factors that may influence decline.

The mean annual decline in forced expiratory volume in 1 s (FEV_1) was 49.9 mL. The greatest FEV_1 decline occurred in the moderate severity group (FEV_1 50–80% of the predicted value), with a mean annual decline of 90.1 mL, compared with 8.1 mL in the very severe group (FEV_1 <30% pred). However, annual decline in transfer coefficient of the lung for carbon monoxide (*K*CO) was greatest in the severe and very severe groups. When the whole group was divided into tertiles of FEV_1 decline, the fast tertile compared with the slow tertile had more patients with bronchodilator reversibility (BDR) (73 *versus* 41%; p=0.010), more males (79 *versus* 56%; p=0.048) and lower body mass index (BMI) (24.0 *versus* 26.1; p=0.042). Logistic regression analyses confirmed that FEV_1 decline was independently associated with BMI, BDR, exacerbation rate and high physical component 36-item short-form health survey scores.

In PiZ α_1-AT-deficient patients, FEV_1 decline was greatest in moderate disease, unlike *K*CO decline, which was greatest in severe disease. The FEV_1 decline showed associations with BDR, BMI, sex and exacerbation rate.

KEYWORDS: α_1-antitrypsin deficiency, chronic obstructive pulmonary disease, disease progression, lung function tests

Progression of emphysema in α_1-antitrypsin (α_1-AT) deficiency (α_1-ATD) is known to occur at an accelerated rate compared with usual chronic obstructive pulmonary disease (COPD) [1, 2]. At present, there is uncertainty regarding which patients show the greatest rate of progression, and, therefore, may show the clearest signal for α_1-AT augmentation trials or response to future treatments. This reflects a lack of knowledge of the natural history of the disease and completion of effective clinical trials of treatment.

Logically, effective preventative therapy should be introduced early in order to prevent subsequent deterioration. However, it is not currently known whether all patients with α_1-ATD deteriorate and at what rate. Index patients identified by presentation to healthcare services exhibit worse lung function than matched non-index siblings [3]. Lifelong nonsmokers show less progression and lower mortality [1, 4], but a significant number develop airflow obstruction in middle age [5]. Nevertheless, many subjects remain unidentified because either the diagnosis has not been considered or they remain clinically well. In order to identify all patients, extensive screening would be necessary, with long-term follow-up, such as in the Swedish cohort study [6].

The variation in progression rate in α_1-ATD patients has also hampered clinical therapy trials since large numbers of subjects need to be studied over a long period of time in order to determine efficacy [7]. However, targeting only patients who are rapidly progressing for such trials would reduce the numbers needed and decrease the necessary duration of the study. Indirect data from the US National Institutes of Health (NIH) registry provide supporting evidence for this concept. The only patients demonstrating a possible benefit of augmentation therapy were those in the moderately affected group with a rapidly declining forced expiratory

For editorial comments see page 1241.

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volume in 1 s (FEV1) [1]. Furthermore, this is supported by the observation that rapid decliners in the German sequential study showed a subsequent slowing of progression following augmentation [8].

The present study was designed to answer several questions. First, it was designed to assess the progression of airflow obstruction and a more specific measure of emphysema (the carbon monoxide transfer factor) in patients with a broad spectrum of physiological impairment; secondly to identify factors that are associated with the decline in lung function, and; finally, to determine factors that are associated with the most rapid decline in order to identify the most appropriate patients for clinical trials and those most likely to benefit from effective interventions.

METHODS

The UK Antitrypsin Deficiency Assessment and Programme for Treatment (ADAPT) programme (funded by a noncomercial grant from Talecris Biotherapeutics Inc., Research Triangle Park, NC, USA) has been collecting data on α_1-ATD patients prospectively since 1996, in order to gain understanding of the natural history of the condition and form a basis for future treatments. None received α_1-AT augmentation therapy, since it is not yet licensed in the UK. At the time of analysis, all patients who had been followed for $\geqslant$3 yrs were identified; 40 patients were excluded because they had less than four consecutive annual lung function measurements including that at baseline. An additional three were excluded because they had received lung transplants. These 43 excluded patients were of milder severity, on average, than those included in the analysis (mean baseline FEV1 70.5% of the predicted value in those excluded compared with 54.3% pred in those included). There were thus 101 patients with a PiZ phenotype on the registry who had had lung function recorded annually over a 3-yr period. Using regression equations, the mean decline in FEV1 and carbon monoxide transfer corrected for lung volume (*K*CO) was calculated over the 3 yrs (four measurements) for each patient. The patients were then divided into groups according to baseline percentage predicted FEV1, equivalent to American Thoracic Society (ATS)/European Respiratory Society (ERS) severity groups for COPD [9]. The mean decline in FEV1 and *K*CO over 3 yrs was then determined for each group. Factors associated with the decline were identified from baseline characteristics by univariate analysis. All correlates were then entered into a linear regression analysis in order to identify independent factors that predicted overall decline. This compared FEV1 and *K*CO decline as continuous variables against the factors, adjusting for age, sex, cumulative smoking exposure and baseline lung function.

In order to identify factors characteristic of rapid decline, the 101 patients as a whole were then separately divided into tertiles according to speed of FEV1 decline. The fast-decline tertile and slow-decline tertile were compared, using univariate and multivariate analyses, for differences in the following parameters, assessed at baseline: sex; body mass index (BMI); acute reversibility to bronchodilator (BDR; defined by ATS criteria; $\geqslant$200 mL change in FEV1 and 12% change from baseline FEV1 after 400 μg inhaled salbutamol [10]); smoking status; chronic bronchitis (UK Medical Research Council criteria [11]); age; health status scores, from the 36-item short-form health survey (SF-36) physical and mental component scores, and St George's Respiratory Questionnaire total score; exacerbation rates characterised as type 1 and 2 as described by ANTHONISEN [12], derived from self-reported retrospective recall on an annual questionnaire; baseline FEV1 (% pred); baseline *K*CO (% pred); and extent of emphysema on computed tomography (CT) scan (inspiratory and expiratory films, lower and upper zones) using the voxel index (-910 HU) as described previously [13].

The 95 out of the 101 patients who had complete *K*CO data were also divided into tertiles according to their rate of *K*CO decline, and univariate and multivariate analyses were performed comparing the fast- and slow-decline tertiles for the same parameters as used in the decline in FEV1 analyses described above.

The lung function equipment used was the MasterScreen PFT (Jaeger, Hoechberg, Germany), and quality control of equipment and technician input was according to ATS/ERS standards [14–16].

High-resolution CT scans were performed, using a GE ProSpeed Scanner (General Electric Medical Systems, Milwaukee, WI, USA) to obtain 1-mm slices. The scanner was calibrated weekly using 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 of $<$-910 HU. The voxel index is the percentage of highlighted voxels with a density below this threshold, reflecting the proportion of emphysematous tissue.

The exacerbation data were obtained from annual questionnaires based on retrospective recall. The questions were as follows. 1) ''Have you had any episodes of increased sputum volume or purulence since the last visit? If yes…How many? Which months?'' 2) ''Have you had any episodes of increased breathlessness since the last visit? If yes…How many? In which months?''. Where the answer was yes to both questions, the number of occasions on which the identified months matched was the number of Antonisen type 1 (all three symptoms) and type 2 exacerbations (two of the three symptoms) during that year [17].

Ethical approval was granted by the Local Research Ethics Committee (University Hospital Birmingham, Birmingham, UK), and all patients gave informed consent for the investigations.

Data analysis

The annual declines in FEV1 and *K*CO for each patient were estimated from all of the data using simple linear regression (SPSS® version 12; SPSS, Inc., Chicago, IL, USA). Multiple linear regression was used to adjust the continuous variables FEV1 decline and *K*CO decline for age, sex, cumulative smoking status and baseline FEV1 or *K*CO, and to investigate the effect of other variables on the adjusted values.

Separately, nonparametric univariate analyses of the fast *versus* slow FEV1 and *K*CO decline tertiles for the parameters of

interest were performed using Mann–Whitney U-tests. Multivariate analyses of FEV1 and *K*CO decline were then performed using forward stepwise logistic regression analysis (SPSS version 12), with the same factors as were entered into the univariate analysis, using fast- or slow-decline tertile as the dependent variable. The significant variables in the stepwise analyses were then included in further logistic regression analyses along with age, sex, cumulative smoking exposure and FEV1 in order to determine whether they remained significant following adjustment for these factors.

RESULTS

For the patients as a whole, the mean decline in FEV1 was 49.9 ± 7.4 mL·yr^{-1}. When divided into severity groups according to baseline percentage predicted FEV1, the fastest mean decline in FEV1 occurred in the moderate severity group (FEV1 50–80% pred) at 90.1 ± 19.7 mL·yr^{-1}. The speed of decline was also faster than average in the severe group (FEV1 30–50% pred) at 51.9 ± 7.6 mL·yr^{-1}, but lower than average in the mild group (FEV1 >80% pred) at 31.6 ± 19.3 mL·yr^{-1} and in the very severe group (FEV1 <30% pred) at 8.1 ± 9.6 mL·yr^{-1}. These results are summarised in figure 1.

However, the results for *K*CO decline differed from those for FEV1. The mean *K*CO decline for the whole group was 0.015 ± 0.004 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}. When divided into severity groups according to baseline percentage predicted FEV1, there was a faster decline in *K*CO in the severe (0.030 ± 0.006 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}) and very severe groups (0.025 ± 0.008 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}) than in the moderate (0.004 ± 0.007 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}) and mild groups (-0.0122 ± 0.012 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}) (fig. 2).

Multiple linear regression of FEV1 decline as a continuous variable on the factors listed in table 1, adjusting for age, sex, cumulative smoking exposure and baseline FEV1, showed baseline *K*CO, upper zone inspiratory CT scan voxel index and BMI were significantly associated with fast decline. BMI was most strongly associated with FEV1 decline ($p=0.008$), and, once this was entered into the model, none of the other possible explanatory variables were significant.

Table 1 shows the results of univariate analysis of parameters that may be associated with FEV1 decline (with p-values) for differences between the fast decline (n=33) and slow decline tertile (n=34). In the fast-decline group, there were more patients with BDR (73 *versus* 41%; $p=0.010$), more males (79 *versus* 56%; $p=0.048$) and a lower BMI (24.0 *versus* 26.1; $p=0.042$). Multivariate analyses comparing the fast- and slow-decline tertiles indicated that the features that were independently predictive of fast decline in FEV1 were BDR, low BMI, high exacerbation rate and a high SF-36 component score (table 2).

Multiple linear regression of *K*CO decline as a continuous variable on the factors listed in table 1, adjusting for age, sex, cumulative smoking exposure and baseline *K*CO, showed that baseline FEV1 and the four CT scan voxel indices were significantly associated with fast decline. The lower zone expiratory CT scan voxel index showed the strongest association with *K*CO decline ($p=0.002$), and, once this was entered into the model, none of the other possible explanatory variables were significant.

Table 3 shows the results of univariate analysis for parameters potentially associated with *K*CO decline, when comparing the fast- and slow-decline tertiles. FEV1 (41.8 *versus* 60.2% pred; $p=0.002$) and mean emphysema voxel index scores on lower zone expiratory scan (47.4 *versus* 33.1%; $p=0.010$) and upper zone expiratory scan (24.2 *versus* 16.6%; $p=0.042$) were

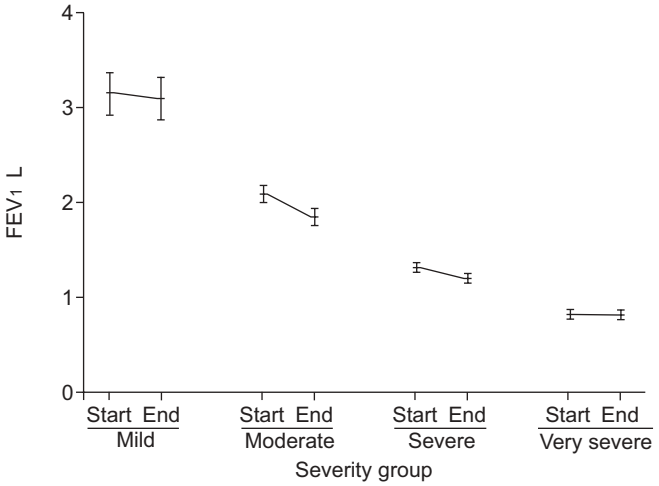

FIGURE 1. Forced expiratory volume in 1 s (FEV1) decline according to severity group based on percentage predicted FEV1 (mild: >80% predicted (31.6 ± 19.3 mL·yr^{-1}; n=18); moderate: 50–80% pred (90.1 ± 19.7 mL·yr^{-1}; n=26); severe: 30–50% pred (51.9 ± 7.6 mL·yr^{-1}; n=38); very severe: <30% pred (8.1 ± 9.6 mL·yr^{-1}; n=19)). Data are presented as mean±SEM FEV1 at the start and end of the 3-yr follow-up. The greatest decline occurred in the moderate severity group. The overall mean decline in FEV1 was 49.9 ± 7.4 mL·yr^{-1}.

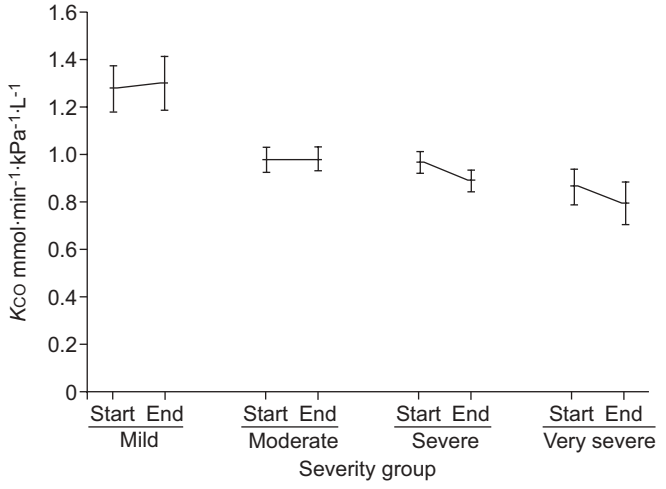

FIGURE 2. Transfer coefficient of the lung for carbon monoxide (*K*CO) decline according to severity group based on percentage predicted FEV1 (mild: >80% predicted (-0.0122 ± 0.012 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}; n=16); moderate: 50–80% pred (0.004 ± 0.007 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}; n=26); severe: 30–50% pred (0.030 ± 0.006 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}; n=36); very severe: <30% pred (0.025 ± 0.008 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}; n=17)). Data are presented as mean±SEM *K*CO at the start and end of the 3-yr follow-up. The greatest decline occurred in the severe and very severe groups. The overall mean decline in *K*CO was 0.015 ± 0.004 mmol·min^{-1}·kPa^{-1}·L^{-1}·yr^{-1}.

TABLE 1 Univariate analysis comparing the fast tertile of decline in forced expiratory volume in 1 s (FEV_1) with the middle and slow tertiles

	Fast	Middle	Slow	p-value#
Subjects n	33	34	34	
M/F n	26/7	22/12	19/15	**0.048**
Age yrs	51.2±8.62	52.7±11.0	49.1±8.57	0.184
Ever-smoker n	26	28	29	0.222
Cumulative smoking history pack-yrs	17.0±13.6	19.8±14.7	18.7±16.6	0.801
Index case n	30	31	26	0.113
BMI kg·m^{-2}	24.0±2.63	26.1±4.01	26.1±4.33	**0.042**
Chronic bronchitis n	13	14	19	0.180
SGRQ total score	49.6±20.1	56.2±18.5	51.6±24.7	0.498
SF-36 physical score	40.3±9.41	33.9±10.5	36.1±12.0	0.063
SF-36 mental score	48.4±13.0	48.7±10.4	49.5±11.0	0.950
Bronchodilator reversibility¶ n	24	24	14	**0.010**
Baseline FEV_1 % pred	60.1±22.7	47.9±24.9	55.0±35.8	0.053
Baseline *K*CO % pred	64.0±21.9	68.9±18.5§	71.6±28.3	0.205
Voxel index %				
Upper zone, inspiratory	37.3±17.7	31.8±15.3	29.9±19.1§	0.070
Upper zone, expiratory	23.2±13.9+	20.1±15.5§	20.6±19.8§	0.238
Lower zone, inspiratory	48.3±19.7	52.2±15.4	43.6±21.4§	0.509
Lower zone, expiratory	37.1±18.3+	43.0±18.0§	36.6±22.1§	0.906
Exacerbation rate events·yr^{-1}	1.61±1.20	1.48±1.07	1.22±0.71	0.267

Data are presented as mean±SD unless otherwise indicated. M: male; F: female; BMI: body mass index; SGRQ: St George's Respiratory Questionnaire; SF-36: 36-item short-form health survey; % pred: % predicted; *K*CO: carbon monoxide transfer corrected for alveolar volume. #: fast *versus* slow tertile (significant values are shown in bold type), ¶: American Thoracic Society criteria; +: n=32; §: n=33.

significantly different between the two groups. When multivariate analyses were performed comparing the fast- and slow-decline tertiles (table 4), the only parameter that was independently predictive of fast decline in *K*CO was FEV_1.

DISCUSSION

The UK database provides a unique opportunity for studying multiple factors in a cohort of highly characterised α_1-ATD patients not receiving augmentation therapy. Those with consecutive annual lung function measurements showed a mean decline in FEV_1 determined by summary statistics over a 3-yr period of 49.9 mL·yr^{-1}. There have been few such studies reported in the literature, although the patients in the placebo group (n=28) in the Dutch/Danish pilot study of α_1-AT augmentation therapy [7] showed a mean decline in FEV_1 of 59.1 mL·yr^{-1} over 3 yrs. In a comparative study between

TABLE 2 Logistic regression analyses with fast/slow tertile of decline in forced expiratory volume in 1 s (FEV_1) as the dependent variable#

	Stepwise logistic regression		Adjusted logistic regression¶	
	OR (95% CI)	p-value+	OR (95% CI)	p-value+
SF-36 physical score	1.102 (1.030–1.180)	**0.005**	1.080 (1.004–1.161)	**0.039**
Exacerbation rate	2.760 (1.245–6.119)	**0.012**	2.725 (1.184–6.271)	**0.018**
BDR§	4.316 (1.300–14.334)	**0.017**	3.997 (1.083–14.748)	**0.038**
BMI kg·m^{-2}	0.818 (0.680–0.984)	**0.033**	0.775 (0.620–0.968)	**0.025**
Female sex			0.445 (0.108–1.839)	0.264
Age yrs			1.005 (0.925–1.091)	0.913
Smoking pack-yrs			1.002 (0.958–1.047)	0.935
FEV_1 % pred			1.016 (0.990–1.044)	0.232

Odds ratios (ORs) relate to the odds of being in the fast tertile. CI: confidence interval; SF-36: 36-item short-form health survey; BDR: bronchodilator reversibility; BMI: body mass index; % pred: % predicted. #: all of the variables listed in table 1 were available for inclusion in the stepwise model, and the variables listed were forced into the adjusted model; ¶: for sex, age, smoking and FEV_1; +: significant values are shown in bold type; §: American Thoracic Society criteria.

TABLE 3 Univariate analysis comparing the fast tertile of transfer coefficient of the lung for carbon monoxide (*K*CO) decline with the middle and slow tertiles

	Fast	Middle	Slow	p-value#
Subjects n	32	31	32	
M/F n	21/11	21/11	20/12	0.796
Age yrs	50.3±7.43	51.7±7.91	51.2±11.2	0.667
Ever-smoker n	28	26	24	0.887
Cumulative smoking history pack-yrs	22.3±15.9	15.2±10.3	18.8±17.6	0.293
Index case n	29	27	26	0.285
BMI kg·m^{-2}	25.1±3.65	24.6±3.28	26.1±4.26	0.468
Chronic bronchitis n	15	15	12	0.451
SGRQ total score	56.6±17.8+	47.6±21.2	54.2±22.3+	0.938
SF-36 physical score	36.3±9.46	48.7±9.36	34.9±12.4	0.493
SF-36 mental score	48.0±11.6	50.4±12.4	48.5±9.71	0.936
Bronchodilator reversibility¶ n	25	15	20	0.175
Baseline FEV1 % pred	41.8±16.4	60.6±32.3	60.2±29.7	**0.009**
Baseline *K*CO % pred	68.1±20.9	67.9±28.0	68.6±22.1	0.952
Voxel index %				
Upper zone, inspiratory	34.1±16.1	37.4±17.0	27.8±18.7	0.087
Upper zone, expiratory	24.2±15.9	23.5±17.8	16.6±15.3	**0.042**
Lower zone, inspiratory	55.0±13.4	47.3±18.0	42.8±23.6	0.067
Lower zone, expiratory	47.4±13.9	36.1±19.6	33.9±22.0	**0.010**
Exacerbation rate events·yr^{-1}	1.42±1.52	1.56±1.05	1.38±1.37	0.673

Data are presented as mean±SD, unless otherwise stated. M: male; F: female; BMI: body mass index; SGRQ: St George's Respiratory Questionnaire; SF-36: 36-item short-form health survey; FEV1: forced expiratory volume in 1 s; % pred: % predicted. #: fast *versus* slow tertile (significant values are shown in bold type), ¶: American Thoracic Society criteria; +: n=31.

Danish patients not receiving α_1-AT augmentation (n=97) and German patients receiving augmentation [18], the Danish group exhibited a mean decline in FEV1 of 75.0 mL·yr^{-1}. In a German study before and after α_1-AT augmentation treatment [8], the pre-treatment group (n=96) showed a decline in FEV1 of 49.2 mL·yr^{-1}. Finally, in a US α_1-AT registry study [1], the mean decline in FEV1 was 56 mL·yr^{-1} in those never receiving α_1-AT augmentation therapy. Thus, with the exception of the Danish/German comparative group [18], data from all of these studies are comparable, despite the wide range of initial FEV1 in the present patients.

The decline is dependent upon several factors. First, it relates to the initial FEV1, and the present data show that the greatest change (90.1 mL·yr^{-1}) occurs in those with an initial moderate FEV1 impairment (50–80% pred), which is comparable with results from the US registry of 81.2 mL·yr^{-1} in those not receiving augmentation therapy [1]. The lack of decline (mean 8.1 mL·yr^{-1}) in the most severe group probably reflects a survivor effect [12], since, by study design, data could only be obtained from patients who survived ⩾3 yrs. Since mortality reflects FEV1 [19–24] it is likely that any rapid decliners in this group would have died during the study period. Why this

TABLE 4 Logistic regression analyses with fast/slow tertile of decline in transfer coefficient of the lung for carbon monoxide (*K*CO) as the dependent variable#

	Stepwise logistic regression		Adjusted logistic regression¶	
	OR (95% CI)	p-value+	OR (95% CI)	p-value+
FEV1 % pred	0.964 (0.938–0.991)	**0.009**	0.964 (0.938–0.991)	**0.009**
Female sex			0.910 (0.269–3.075)	0.879
Age yrs			0.977 (0.916–1.043)	0.490
Smoking pack-yrs			0.999 (0.967–1.033)	0.965

Odds ratios (ORs) relate to the odds of being in the fast tertile. CI: confidence interval; FEV1: forced expiratory volume in 1 s; % pred: % predicted. #: all of the variables listed in table 3 were available for inclusion in the stepwise model, and the variables listed were forced into the adjusted model; ¶: for sex, age and smoking; +: significant values are shown in bold type.

observation is at variance with data from the NIH report for a similar group (mean decline of 46.5 mL·yr^{-1} in those with an FEV1 of <35% pred not receiving augmentation therapy) remains unknown, especially since the median follow-up time was longer (52 months) in the NIH study.

When FEV1 decline was compared as a continuous variable, correcting for various confounding factors, BMI was found to show the best association in this more general analysis. In order to identify a specific subset at risk of rapid decline, comparison was made between the two extreme tertiles of decline. This has implications for both selection of patients for clinical trials of potential interventions and early introduction of effective therapies. Many factors were found to be associated with more-rapid decline in these analyses. The finding that FEV1 decline was greater in patients with BDR and in males is in agreement with data from the US registry [1]. Lower BMI has been linked with greater progression of disease and mortality in α_1-ATD [25] and usual COPD [26]. In the logistic multivariate analysis, BDR, low BMI and exacerbation frequency were found to be independent predictors of decline in FEV1.

Exacerbation frequency is known to relate to a speedier decline in lung function in α_1-ATD [27] and usual COPD [26]. However, the relationship with better physical health status may at first seem counter-intuitive. The most severely restricted patients, however, are those with the lowest FEV1, and the reduced FEV1 decline in this group probably explains the association. Nevertheless, with all of these confounding factors, differences in any may explain the greater rate of progression seen in the untreated group in the Danish/German comparative study, as well as possibly the range of initial impairment [18].

The data differed for *K*CO decline, which was greatest in patients with severe disease, as defined by baseline percentage predicted FEV1. This would suggest that rapid decline in gas transfer is a late phenomenon in disease progression. Unlike FEV1 decline, which largely reflects bronchial disease, *K*CO decline reflects alveolar destruction alone. The analyses confirmed that only factors associated with disease severity (baseline FEV1 and CT voxel indices) were significantly associated with *K*CO decline. Recent studies have shown that emphysema distribution relates differentially to FEV1 and *K*CO [28, 29]. Emphysema in α_1-ATD tends to dominate in the lower zones and spread to the upper zones as disease progresses. Lower-zone emphysema has been shown to affect FEV1 more than *K*CO, and upper-zone emphysema has the opposite effect. Therefore, it might be expected that *K*CO decline would become more pronounced in more severe disease as emphysema progresses from the bases to involve the upper zones, as found here.

These data provide information central to the identification of fast decliners. For FEV1, the decline is greatest in moderate-to-severe disease, and, in this group, BDR, low BMI and increased exacerbation frequency independently predict the rate. Thus, if FEV1 decline is the primary outcome, patients with these characteristics would be best recruited for the testing of interventional strategies and instigation of effective preventative therapy.

Although *K*CO is a more specific measure of emphysema, it progresses most rapidly in the most severe groups. At this point, physiological impairment is well established and it is unlikely that gas transfer would be an effective marker for identifying rapid decliners early enough in the disease to be effective or provide a robust group for long-term studies for determining the efficacy of new treatments.

In the current study, CT scans were not available for all patients over the 3 yrs. However, other studies have shown that this parameter alone shows progression independent of disease stage [30]. This reinforces its use as a primary outcome measure, especially since it is the best indirect measure of pathological emphysema. If the efficacy of specific interventions is confirmed using CT scores as an outcome, it is also likely to become the measure of choice in determining rapid progression before physiological tests become adversely affected.

The current study had some limitations. The analysis was performed only on those patients for whom four consecutive annual pulmonary function test results were available, in order to obtain the most accurate regression data. Therefore, patients were excluded who did not have consecutive lung function tests performed because of missed appointments, withdrawal from the programme or death. Exclusion of this latter group, in particular, could modify the associations with declining lung function towards factors that influence survival (the healthy survivor effect). The results of the logistic regression analyses compared the fast and slow tertiles of lung function decline, with the aim of identifying differences between the two extreme groups, but, when a separate linear regression analysis was undertaken assessing lung function decline as a continuous variable, the results were slightly different. Most data were determined objectively, but the exacerbation data relied upon subjective recall, and, since the patients were visiting the centre from all parts of the country, independent verification of exacerbations and hospitalisations from health records was impossible. Nevertheless, when diary card identification and primary care records have been assessed, such recall has proven reasonably reliable [27], suggesting that the associations found here are likely to be valid.

In summary, it has been shown that, in a group of PiZ phenotype α_1-ATD patients, FEV1 decline was greatest in those with moderately severe disease, and this showed associations with BDR, BMI, male sex and (in a multiple regression analysis) exacerbation rate. *K*CO decline, conversely, was greatest in severe disease, and was only associated with other measures of disease severity (FEV1 and CT densitometry). These findings have implications for the subgroups of patients to target in future clinical trials, and the stage at which effective therapy should be targeted.

REFERENCES

1 Survival and FEV1 decline in individuals with severe deficiency of α_1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. *Am J Respir Crit Care Med* 1998; 158: 49–59.

2 Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological, and health status measurements in α_1-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med* 2001; 164: 1805–1809.

3 Needham M, Stockley RA. α_1-Antitrypsin deficiency. 3: Clinical manifestations and natural history. *Thorax* 2004; 59: 441–445.
4 Larsson C. Natural history and life expectancy in severe α_1-antitrypsin deficiency, Pi Z. *Acta Med Scand* 1978; 204: 345–351.
5 Piitulainen E, Tornling G, Eriksson S. Effect of age and occupational exposure to airway irritants on lung function in non-smoking individuals with alpha 1-antitrypsin deficiency (PiZZ). *Thorax* 1997; 52: 244–248.
6 Wu MC, Eriksson S. Lung function, smoking and survival in severe alpha 1-antitrypsin deficiency, PiZZ. *J Clin Epidemiol* 1988; 41: 1157–1165.
7 Dirksen A, Dijkman JH, Madsen F, *et al.* A randomized clinical trial of α_1-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999; 160: 1468–1472.
8 Wencker M, Fuhrmann B, Banik N, *et al.* Longitudinal follow-up of patients with α_1-protease inhibitor deficiency before and during therapy with IV α_1-protease inhibitor. *Chest* 2001; 119: 737–744.
9 Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
10 American Thoracic Society, Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.
11 Definition and classification of chronic bronchitis for clinical and epidemiological purposes. A report to the Medical Research Council by their Committee on the Aetiology of Chronic Bronchitis. *Lancet* 1965; 1: 775–779.
12 Anthonisen NR. Prognosis in chronic obstructive pulmonary disease: results from multicenter clinical trials. *Am Rev Respir Dis* 1989; 140: S95–S99.
13 Dawkins PA, Dowson LJ, Guest PJ, *et al.* Predictors of mortality in α_1-antitrypsin deficiency. *Thorax* 2003; 58: 1020–1026.
14 Macintyre N, Crapo RO, Viegi G, *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005; 26: 720–735.
15 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
16 Wanger J, Clausen JL, Coates A, *et al.* Standardisation of the measurement of lung volumes. *Eur Respir J* 2005; 26: 511–522.
17 Anthonisen NR, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
18 Seersholm N, Wencker M, Banik N, *et al.* Does α_1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary α_1-antitrypsin deficiency? *Eur Respir J* 1997; 10: 2260–2263.
19 Ebi-Kryston KL. Respiratory symptoms and pulmonary function as predictors of 10-year mortality from respiratory disease, cardiovascular disease, and all causes in the Whitehall Study. *J Clin Epidemiol* 1988; 41: 251–260.
20 Hole DJ, Watt GC, Davey-Smith G, *et al.* Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; 313: 711–715.
21 Krzyzanowski M, Wysocki M. The relation of thirteen-year mortality to ventilatory impairment and other respiratory symptoms: the Cracow Study. *Int J Epidemiol* 1986; 15: 56–64.
22 Peto R, Speizer FE, Cochrane AL, *et al.* The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983; 128: 491–500.
23 Tockman MS, Comstock GW. Respiratory risk factors and mortality: longitudinal studies in Washington County, Maryland. *Am Rev Respir Dis* 1989; 140: S56–S63.
24 Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15- year follow-up study. *Am Rev Respir Dis* 1979; 119: 895–902.
25 Seersholm N. Body mass index and mortality in patients with severe α_1-antitrypsin deficiency. *Respir Med* 1997; 91: 77–82.
26 Donaldson GC, Seemungal TA, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
27 Needham M, Stockley RA. Exacerbations in α_1-antitrypsin deficiency. *Eur Respir J* 2005; 25: 992–1000.
28 Holme J, Stockley RA. Radiologic and clinical features of COPD patients with discordant pulmonary physiology. Lessons from α_1-antitrypsin deficiency. *Chest* 2007; 132: 909–915.
29 Parr DG, Stoel BC, Stolk J, *et al.* Pattern of emphysema distribution in α_1-antitrypsin deficiency influences lung function impairment. *Am J Respir Crit Care Med* 2004; 170: 1172–1178.
30 Stolk J, Putter H, Bakker EM, *et al.* Progression parameters for emphysema: a clinical investigation. *Respir Med* 2007; 101: 1924–1930.