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Exacerbations in α_1-antitrypsin deficiency

M. Needham and R.A. Stockley

ABSTRACT: This study aimed to investigate the nature and effect of exacerbations in patients with α_1-antitrypsin deficiency and to assess the impact of exacerbations on health status. Furthermore, the relationship of exacerbations to changes in lung function and health status was investigated.

In total, 265 patients with severe deficiency (PiZ phenotype) were assessed over 12 months and a subgroup of 87 patients was studied for 3 yrs. Exacerbations were recorded and patients underwent full lung function testing and health status measurement.

Exacerbations occurred in 142 patients (54%) over 12 months, with a median duration of 14 days (interquartile range 7–21). Health status was significantly worse in patients with exacerbations, especially those with frequent exacerbations. Neither the presence nor the frequency of exacerbations showed a relationship to decline in forced expiratory volume in one second, but the number of exacerbations was weakly associated with decline in gas transfer of the lung for carbon monoxide. Despite lung function decline, health status did not change significantly over 3 yrs.

In conclusion, exacerbations occur commonly in patients with α_1-antitrypsin deficiency and are associated with worse health status. Exacerbations were associated with a decline in the gas transfer of the lung for carbon monoxide over time, but show no relationship to changes in forced expiratory volume in one second. Despite lung function decline, patients do not show a progressive loss in health status.

KEYWORDS: α_1-antitrypsin deficiency, chronic obstructive pulmonary disease, health status, respiratory tract infections

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Exacerbations of chronic obstructive pulmonary disease (COPD) place a significant burden on healthcare resources and expenditure [1]. Furthermore, exacerbations adversely affect patients and more frequent exacerbations have been shown to be related to worse quality of life (QoL) [2]. Exacerbations in patients with usual COPD are well documented, but less is known about the occurrence, time course and effect of exacerbations in patients with α_1-antitrypsin deficiency (AATD).

Enhanced decline in lung function is well recognised in AATD [3, 4] and it has been suggested in a small study that exacerbation frequency may influence this decline [5]. It is possible, therefore, that interventions that reduce the frequency of exacerbations may also modify the decline. Indeed, α_1-antitrypsin augmentation therapy, which may modulate lung function decline in some patients [3], may also be associated with a reduction in the frequency and severity of exacerbations [6], although prospective clinical trials are required to support this assumption.

In order to design and power relevant clinical trials in AATD, more detailed information concerning the number, nature, timing and consistency of exacerbations and their effect on health status is essential. Many clinical trials now include these measures as valid outcomes and so documentation of changes in health status over time is also essential, as well as an understanding of how exacerbations may affect this change.

For these reasons, 265 patients with AATD were studied to investigate the frequency, duration, timing and nature of exacerbations and to identify any host factors that may be associated with these episodes. The impact of exacerbations on health-related QoL was also investigated, as measured by the Short-Form 36 (SF36) [7, 8] and the St George's Respiratory Questionnaire (SGRQ) [9] in this patient cohort. Furthermore, the change in lung function and health status over 3 yrs was assessed in a subgroup of 87 patients and the influence of exacerbations on these changes was investigated.

METHODS AND MATERIALS

Subjects

The first 265 patients with PiZ deficiency recruited to the authors' database from 1996

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were studied prospectively at a single centre. All patients had a serum α_1-antitrypsin level of <11 μM and had PiZ phenotype confirmed by isoelectric focusing (Heredilab, Salt Lake City, UT, USA). Informed and written consent was obtained and patients were assessed at an initial baseline visit and 12 months later. In total, 90 patients were assessed annually for a further 2 yrs, although one patient underwent lung transplantation during this time and was removed from the 3-yr analysis. Two patients continued to smoke during this 3-yr period and were also removed from the analysis to maximise patient homogeneity. None of the subjects received α_1-antitrypsin augmentation therapy. Data on 117 of these patients has been published previously in a more limited study [10].

Clinical history

At baseline, a full clinical history was taken to include respiratory symptoms, smoking history and the presence of chronic bronchitis (Medical Research Council criteria [11]). Patients were classified as index cases if their symptoms had led to the diagnosis of AATD and non-index if they were diagnosed through family screening.

On annual subsequent visits, details of the occurrence and nature of exacerbations of respiratory symptoms over the previous year were obtained. The length and time of year of the first four episodes were noted from patient recall, with corroboration from diary cards where possible. Exacerbations were defined as acute episodes of worsening symptoms and the duration was taken as the length of time from onset up to the last day before the patient was back to their usual state. Exacerbations were categorised according to the Anthonisen classification [12]: type-1 exacerbations were defined as those with increased dyspnoea, sputum volume and sputum purulence; type-2 exacerbations occurred when two of these symptoms were present; and type-3 exacerbations when only one symptom was present. Frequent exacerbations were defined as $\geqslant$3 episodes over a 12-month period. The incidence of exacerbations was documented annually for the patients who were followed for 3 yrs.

Lung function testing

At the first visit (at least 4 weeks after an exacerbation) patients performed spirometry and bronchodilator reversibility following nebulised 5 mg β_2-agonist and 500 μg ipratropium bromide [13]. Positive bronchodilator reversibility was taken to be an increase of >200 mL and >12% predicted [14]. At subsequent visits, spirometry was repeated after dual bronchodilatation and changes in lung function were derived from all post-bronchodilator values. Lung-volume measurements were assessed using helium dilution (Morgan Medical, Kent, UK) and gas transfer by the single-breath carbon monoxide method. Predicted values were calculated using the equations from the British Thoracic Society/Association of Respiratory Technicians and Physiologists guidelines for respiratory function [15].

Health status

SGRQ was used as a disease-specific tool, with a high score indicating worse health status and a clinically important change in total score being greater than four points [16]. The generic SF36 was also used (low score indicating worse health status), although no threshold for a clinically significant change has been validated. Data were recorded at each visit without reference to previous answers.

Changes over 3 yrs

Changes in lung function tests over 3 yrs were calculated using linear regression on the four measurements taken for each individual over that time and then converted into a change per year. Similar calculations were performed to obtain values for health status changes.

Statistical analysis

Parametric data are displayed as mean$\pm$SE and nonparametric data as median (interquartile range; IQR). In some instances nonparametric data was also presented as mean$\pm$SE for comparison with data published by other groups. Repeated measures at two time points were compared using the Wilcoxon signed-rank test. Subgroup comparisons were made using the Mann-Whitney U-test for two groups and Jonckheere-Terpstra test for three and four groups. Pearson's coefficients were used for correlations between continuous variables and frequency comparisons were made using the Chi-squared test. Binary logistic regression was used to test for independent predictors of exacerbations and stepwise linear regression was used to identify independent factors associated with changes in lung function parameters and health status. Statistical significance was accepted at $p<0.05$.

RESULTS

Baseline characteristics

Of the 265 PiZ patients, 167 (63%) were male and 210 (79%) were index cases. In total, 187 patients (72%) were ex-smokers and 17 (6%) continued to smoke during the first year. Chronic bronchitis was diagnosed in 110 (42%) patients. Inhaled steroids were used by 146 patients consistently throughout the initial 12-month period. Thirteen patients had steroid therapy changed during this 12-month period and were removed from the analysis related to the influence of this treatment. The baseline characteristics, lung function data and health status scores of the whole group are shown in table 1.

Lung function data was obtained from 259 patients as six did not wish to undergo testing. Measurements ranged from normal to severe airflow obstruction and markedly impaired gas transfer. Health status scores also showed a wide variation at baseline.

Exacerbations

During the first year of study, exacerbations occurred in 142 subjects (54%) and 47 (18%) had frequent ($\geqslant$3) exacerbations. One patient described 30 exacerbations over 12 months and was excluded from the analysis. The median number of exacerbations for the whole group was 1 (IQR 0–2) or a mean of 1.2 ($\pm$0.1), although for those patients who experienced $\geqslant$1 exacerbation the median number was 2 (IQR 1–3) or a mean of 2.5$\pm$0.2. Type-1 exacerbations were experienced in 89 patients, 44 had type-2 exacerbations, two had both type-1 and type-2 exacerbations and seven patients had type-3 exacerbations during this year.

Exacerbations were experienced throughout the year but were more frequent in the winter months, with 32% of episodes occurring in December and January (fig. 1).

TABLE 1 Baseline characteristics, lung function values and health status scores for the whole patient group, patients with and without exacerbations over the first year and for the group followed for 3 yrs

	All patients	Patients with no exacerbations over year 1	Patients with ⩾1 exacerbation over year 1	p-value#	Subgroup studied for 3 yrs
Subject n	265	123	142		87
Age yrs	49.9±0.6	50.0±1.0	49.9±0.8	NS¶	50.2±1.0
Body mass index kg·m^{-2}	25.0 (22.9–27.8)	25.1 (23.2–27.8)	24.8 (22.2–27.8)	NS	25.0 (23.0–27.0)
Smoking history pack-yrs	13.0 (1.4–24.0)	12.0 (0.5–22.8)	14.6 (4.0–26.0)	NS	17.5 (0–25.0)
Smoking status					
Current	17	8	9	NS+	0
Ex	187	84	103		65
Never	61	31	30		22
Sex					
Male	167	80	87	NS+	59
Female	98	43	55		28
Presentation					
Index	210	90	120	0.023+	67
Non-index	55	33	22		20
Chronic bronchitis					
Yes	110	39	71	0.003+	35
No	155	84	71		52
Inhaled steroid use over initial 12 months					
Yes	146	56	90	0.002+	47
No	106	64	42		37
Altered	13	3	10		3
Bronchodilator reversibility					
Yes	65	23	42	0.034+	23
No	198	100	98		63
FEV_1 L	1.53 (1.02–2.45)	1.77 (1.11–2.93)	1.42 (0.98–2.16)	0.005	
FEV_1 % pred	46.2 (33.8–76.8)	55.2 (35.6–95.3)	43.3 (32.9–68.5)	0.013	
VC L	4.13 (3.16–4.99)	4.28 (3.66–5.11)	3.97 (2.85–4.92)	0.049	
VC % pred	103.5 (91.4–117.3)	106.9 (95.6–119.9)	101.7 (87.6–115.9)	0.044	
RV L	2.58 (2.04–3.24)	2.51 (2.00–3.16)	2.72 (2.18–3.42)	0.037	
RV % pred	129.7 (102.6–155.1)	126.1 (99.7–148.9)	137.4 (106.7–173.8)	0.008	
TLC L	7.40 (6.06–8.40)	7.38 (6.20–8.54)	7.47 (5.91–8.37)	NS	
TLC % pred	119.0 (107.4–130.5)	118.4 (107.7–128.1)	119.1 (108.1–132.6)	NS	
RV/TLC %	36.4 (29.4–43.0)	34.3 (28.0–41.5)	38.9 (32.4–45.5)	0.002	
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	6.37 (4.65–8.27)	6.60 (4.99–8.46)	5.86 (4.29–7.85)	0.035	
$T_{L,CO}$ % pred	68.0 (52.0–85.0)	72.0 (55.0–88.0)	63.6 (50.0–83.0)	0.055	
$T_{L,CO}/V_A$ mmol·min^{-1}·kPa^{-1}·L^{-1}	1.08 (0.80–1.39)	1.12 (0.80–1.44)	1.00 (0.78–1.35)	NS	
$T_{L,CO}/V_A$ % pred	67.9 (53.7–86.0)	69.0 (55.0–87.0)	66.2 (51.0–85.7)	NS	
SGRQ					
Total	51.6 (31.5–65.3)	45.3 (25.1–58.2)	55.4 (38.0–68.7)	<0.001	
Symptoms	64.0 (44.1–78.8)	57.7 (36.8–72.6)	70.9 (53.6–83.8)	<0.001	
Activity	66.2 (41.4–85.9)	59.5 (35.2–79.7)	72.8 (48.5–92.6)	<0.001	
Impacts	36.8 (20.0–52.5)	31.8 (14.7–46.3)	41.5 (25.2–56.8)	<0.001	
SF36					
Physical	37.7 (28.9–45.9)	40.5 (32.6–49.7)	34.0 (26.7–42.5)	<0.001	
Mental	53.2 (45.2–58.7)	53.3 (46.4–58.8)	53.1 (42.5–58.5)	NS	

Data are presented as mean±SE or median (interquartile range), unless otherwise stated. NS: nonsignificant; FEV_1: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity; RV: residual volume; TLC: total lung capacity; $T_{L,CO}$: gas transfer of the lung for carbon monoxide; V_A: alveolar volume; SGRQ: St George's Respiratory Questionnaire; SF36: Short-Form 36. #: univariant comparison of those with and without exacerbations; ¶: t-test; +: Chi-squared test. All other statistical comparisons used the Mann-Whitney U-test.

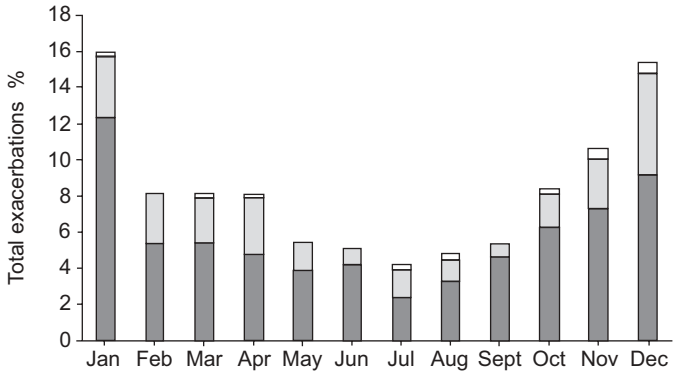

FIGURE 1. The proportion (%) of exacerbations occurring in each month of the year. Exacerbations are categorised by Anthonisen criteria into type 1 (■), type 2 (▩) and type 3 (□).

Episodes varied in length from 2 to >35 days, with a median length of each episode of 14 days (IQR 7–21) (fig. 2).

Exacerbations and baseline characteristics

Exacerbations occurred more frequently in those patients with chronic bronchitis (1.7±0.2 *versus* 1.2±0.2, Chi-squared: p<0.001). Index patients were more likely to have exacerbations compared to non-index patients (1.6±0.2 *versus* 0.8±0.2, Chi-squared: p=0.016). There was no relationship between the number of exacerbations and age, sex or body mass index (BMI). However, a weak correlation was seen between the number of pack-yrs smoked and the number of exacerbations (r=0.12; p=0.03).

Patients with more severe airflow obstruction, as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [17, 18], had more frequent exacerbations (Jonckheere-Terpstra: p=0.002) over the study period, although the median value did not change. Furthermore, patients using inhaled steroids consistently throughout the 12 months had more exacerbations than those who were consistent non-users (Chi-squared: p=0.004) as did those with bronchodilator reversibility (Chi-squared: p=0.042).

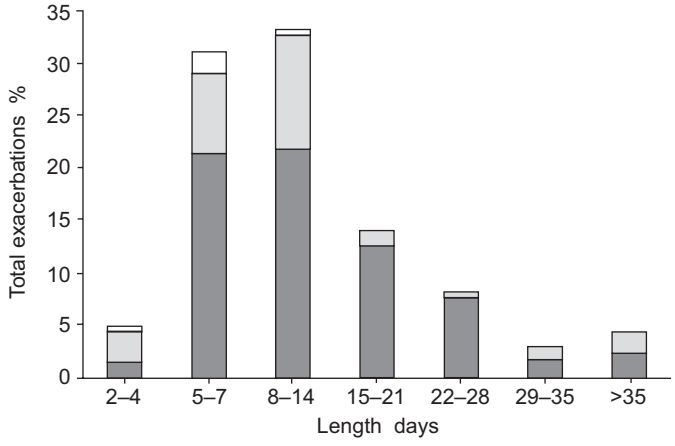

FIGURE 2. The length of exacerbations of symptoms illustrated against proportion of the total (%) for each time period. Exacerbations are categorised by Anthonisen criteria into type 1 (■), type 2 (▩) and type 3 (□).

Univariate comparisons of baseline characteristics, lung function data and health status scores of those with and without exacerbations are displayed in table 1.

Binary logistic regression was performed using all of the patient demographic data, lung function and smoking history. The presence of chronic bronchitis, bronchodilator reversibility and increased air trapping, as measured by residual volume (RV)/total lung capacity (TLC), were all independent predictors of exacerbations (estimated r^2=0.13). For those patients with exacerbations, greater BMI, females, increasing age and lower forced expiratory volume in one second (FEV1) were all predictors of type-1 exacerbations (estimated r^2=0.17).

Exacerbations, lung function and health status

A clear relationship was seen between the number of exacerbations and SGRQ total score (r=0.41; p<0.001; fig. 3) and SF36 physical score (r=-0.33; p<0.001). Patients with more severe airflow obstruction (GOLD criteria) had worse SGRQ health status scores and SF36 physical component scores (all p<0.001; fig. 4).

Linear regression of SGRQ total scores at month 12 showed that lower FEV1, number of exacerbations, increasing age, increase in pack-yr smoking history and the presence of chronic bronchitis were all independent factors associated with worse SGRQ total score and together accounted for 54% of the overall variability in the score.

Lung function data and health status scores at month 12 are displayed in table 2.

Subjects studied for 3 yrs

The baseline characteristics of this subgroup are shown in table 1. In total, 59 patients (68%) were male, 67 (77%) were

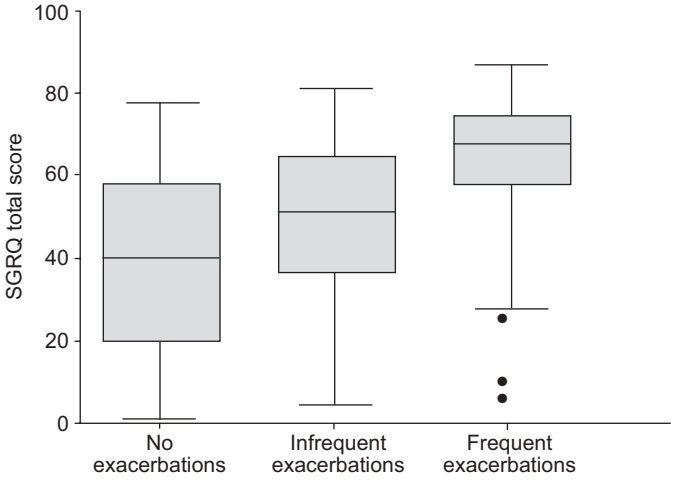

FIGURE 3. Box and whisker plots showing St George's Respiratory Questionnaire (SGRQ) total score at month 12 in patients with no, infrequent and frequent exacerbations. Horizontal black lines show the median values, boxes are interquartile ranges, whiskers show the total range and circles (●) are outliers. Compared with those patients without episodes, higher scores, indicating worse health status, are found in patients with infrequent exacerbations and even higher scores in those with frequent exacerbations (Jonckheere-Terpstra: p<0.001).

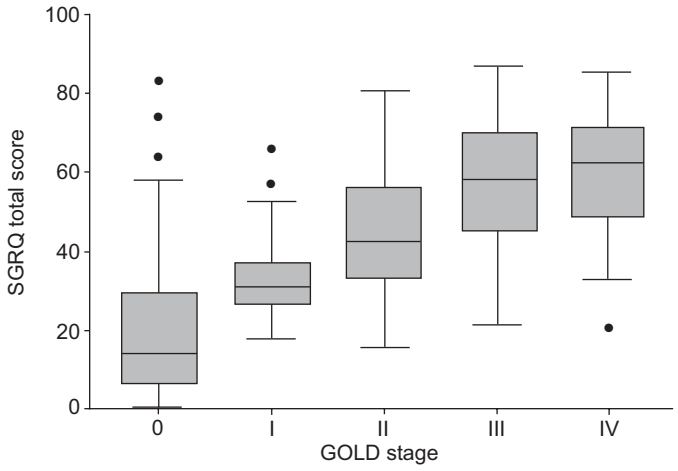

FIGURE 4. Box and whisker plots showing the St George's Respiratory Questionnaire (SGRQ) total score at month 12 in patients grouped according to their Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. Stage 0: n=50; I: n=14; II: n=60; III: n=87; IV: n=48. Horizontal black lines show median values, boxes are interquartile ranges, whiskers show the total range and circles (●) indicate outliers. Significantly worse scores are seen in those patients with greater airflow obstruction (Jonckheere-Terpstra: p<0.001).

index cases, 65 (75%) were ex-smokers and the remainder were never-smokers.

Lung function progression and health status changes

FEV1 showed a significant decline (p<0.001) with a median change of -41 mL·yr^{-1} (IQR -96– -15) over 3 yrs, which reflects an average change of 57±7.5 mL·yr^{-1}. RV measurements and air trapping (as measured by RV/TLC ratio) showed significant increases (p<0.001) over the 3-yr period, whereas gas transfer measurements showed a significant decline (p<0.001). The data obtained at baseline and year 3 are summarised in table 3.

Over the 3 yr period, there was no significant change in SGRQ total, activity and impact scores or in the SF36 scores. However, the SGRQ symptom score showed a significant improvement (p=0.003) over this period of time with a median change of -2.0 units·yr^{-1} (IQR -6.2–1.6; table 3). This improvement in symptom score was progressive from baseline values of 66.4 (37.5–84.3); 64.7 (41.1–81.8) by year 1; 61.8 (40.4–81.8) by year 2; and 61.4 (37.9–74.3) by year 3.

Exacerbations over 3 yrs

The mean number of exacerbations reported for all patients was 1.0±0.2 in the first year, 1.3±0.2 in year 2 and 1.2±0.2

TABLE 2 Lung function data and health status scores at the 12-month visit for the whole patient group and patients with and without exacerbations over year 1

	All patients	Patients with no exacerbations over year 1	Patients with ⩾1 exacerbation over year 1	p-value#
Subjects n	265	123	142	
FEV1 L	1.49 (0.97–2.31)	1.66 (1.04–2.78)	1.41 (0.96–2.06)	0.008
FEV1 % pred	46.6 (33.0–74.9)	52.6 (35.2–94.8)	43.0 (31.6–65.7)	0.014
VC L	4.08 (3.19–4.97)	4.42 (3.58–5.13)	3.79 (2.95–4.83)	0.005
VC % pred	104.3 (90.7–118.5)	107.9 (97.3–122.3)	102.5 (86.3–113.1)	0.004
RV L	2.66 (2.02–3.28)	2.51 (1.90–3.28)	2.70 (2.19–3.32)	NS
RV % pred	127.5 (103.2–162.9)	123.7 (96.0–150.0)	132.3 (107.7–170.2)	0.013
TLC L	7.24 (6.16–8.62)	7.20 (6.20–8.71)	7.26 (6.01–8.51)	NS
TLC % pred	118.7 (107.7–131.0)	118.3 (107.1–130.0)	119.9 (108.0–131.5)	NS
RV/TLC %	37.5 (29.9–44.1)	34.2 (28.3–42.5)	38.8 (32.9–45.8)	0.004
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	6.22 (4.57–8.08)	6.40 (4.66–8.25)	6.07 (4.42–7.93)	NS
$T_{L,CO}$ % pred	66.0 (50.0–82.0)	68.0 (51.0–84.5)	65.0 (50.0–81.0)	NS
$T_{L,CO}/V_A$ mmol·min^{-1}·kPa^{-1}·L^{-1}	1.02 (0.79–1.37)	1.09 (0.80–1.38)	1.01 (0.78–1.32)	NS
$T_{L,CO}/V_A$ % pred	66.2 (52.0–84.0)	68.1 (53.0–85.1)	65.1 (52.0–83.0)	NS
SGRQ				
Total	49.5 (31.0–64.0)	42.0 (22.2–57.3)	56.4 (39.2–70.2)	<0.001
Symptoms	60.7 (38.8–75.0)	40.3 (20.1–61.6)	70.8 (59.0–81.7)	<0.001
Activity	66.2 (41.4–87.2)	57.3 (35.5–79.7)	73.0 (47.9–92.5)	<0.001
Impacts	36.4 (18.7–52.3)	28.2 (13.6–46.2)	40.9 (25.2–55.6)	<0.001
SF36				
Physical	36.7 (28.3–45.4)	39.4 (31.2–48.7)	34.4 (26.2–43.8)	0.001
Mental	54.8 (47.5–59.2)	55.4 (48.6–59.2)	54.2 (46.0–59.3)	NS

Data are presented as median (interquartile range). NS: nonsignificant; FEV1: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity; RV: residual volume; TLC: total lung capacity; $T_{L,CO}$: gas transfer of the lung for carbon monoxide; V_A: alveolar volume; SGRQ: St George's Respiratory Questionnaire; SF36: Short-Form 36. Statistical comparison used the Mann-Whitney U-test. #: univariant comparison of those with and without exacerbations.

for year 3. The proportion of patients having exacerbations remained consistent over the 3 yrs and patients with exacerbations in the first year were more likely to continue having exacerbations in year 2 ($p=0.04$) and year 3 ($p<0.001$). At least one exacerbation had occurred in 50.6% of patients in the first year, 75.9% by year 2 and 80.5% by year 3. Frequent exacerbations (≥ 3 episodes per year) were seen in 12.6% of patients in the first year, 19.0% in year 2 and 13.8% in year 3.

Exacerbations, changes in lung function and changes in health status

Neither the presence nor the frequency of exacerbations over the 3 yrs showed a relationship to the absolute decline in FEV_1 or FEV_1 decline expressed as a % predicted. Furthermore, exacerbations did not have an effect on the decline in FEV_1 when patients were grouped according to baseline airflow obstruction (GOLD criteria). However, a significant correlation was seen between frequency of exacerbations and decline in gas transfer of the lung for carbon monoxide ($T_{L,CO}$) expressed as a % pred ($r=-0.19$; $p=0.037$).

Greater improvement in SGRQ symptom score was seen in those patients who had infrequent or no exacerbations ($p=0.029$; fig. 5). When patients were grouped according to baseline airflow obstruction (GOLD criteria), no significant differences in the change in health status were seen between the groups.

Worsening SGRQ activity score was, however, related to the decline in FEV_1 ($r=-0.24$; $p=0.015$) and to decline in vital capacity ($r=-0.23$; $p=0.017$). Finally, although total scores did not change, a significant correlation was also seen between the changes in SGRQ total score and increased air trapping as measured by the RV/TLC ratio ($r=0.20$; $p=0.037$).

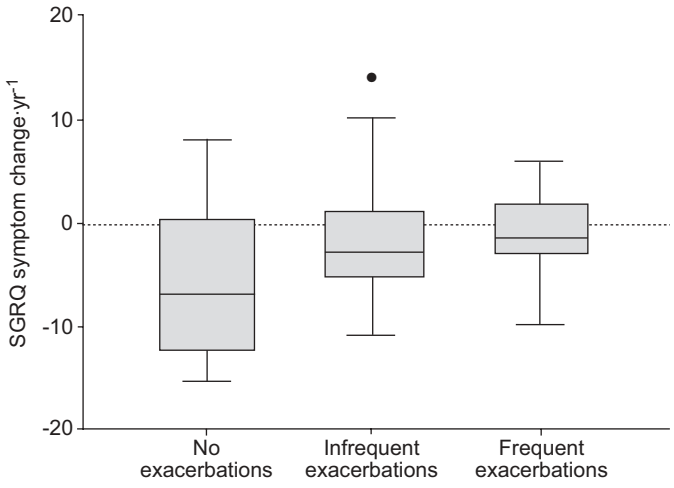

FIGURE 5. Box and whisker plots showing the annual change in St George's Respiratory Questionnaire (SGRQ) symptom score over 3 yrs in patients with no (n=17), infrequent (n=51) and frequent (n=14) exacerbations. Horizontal black lines show the median values, boxes are interquartile ranges, whiskers show the total range and circles (●) are outliers. Greater improvement is seen in patients with fewer exacerbations (Jonckheere-Terpstra: p=0.029).

TABLE 3 Lung function data and health status scores at baseline, the end of year 3 and the change per year as calculated by linear regression using annual results over the 3 yrs

	Subjects n	Baseline	Year 3	Annual change
FEV_1 L	87	1.57 (1.00–2.43)	1.32 (0.88–2.22)	-0.041 (-0.096– -0.015)
FEV_1 % pred	87	48.5 (33.1–87.8)	41.6 (31.1–81.5)	1.0 (-2.5–0.1)
VC L	87	4.09 (3.25–4.83)	3.90 (3.29–4.71)	-0.052 (-0.120–0.006)
VC % pred	87	105.3 (94.5–120.5)	106.2 (87.1–122.9)	-0.5 (-2.2–1.4)
RV L	81	2.52 (2.00–3.24)	2.70 (2.05–3.37)	0.064 (-0.034–0.172)
RV % pred	81	126.5 (97.0–154.8)	133.7 (101.8–169.7)	1.7 (-3.3–7.9)
TLC L	81	7.28 (6.14–8.22)	7.21 (6.02–8.46)	0.029 (-0.117–0.148)
TLC % pred	81	118.9 (104.7–132.1)	117.4 (105.8–134.2)	0.5 (-1.9–2.4)
RV/TLC %	81	35.5 (29.2–42.3)	39.5 (30.5–44.8)	0.6 (-0.3–2.0)
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	87	6.24 (4.67–8.32)	5.39 (4.11–7.16)	-0.21 (-0.37– -0.04)
$T_{L,CO}$ % pred	87	66.0 (53.0–88.0)	61.0 (46.5–80.5)	-1.8 (-3.6– -0.2)
$T_{L,CO}/V_A$ mmol·min^{-1}·kPa^{-1}·L^{-1}	87	1.06 (0.77–1.41)	0.99 (0.72–1.33)	-0.03 (-0.05–0)
$T_{L,CO}/V_A$ % pred	87	67.2 (53.3–91.8)	64.5 (46.5–85.8)	-2.0 (-3.7– -0.7)
SGRQ				
Total	86	52.5 (27.8–66.6)	50.0 (29.3–67.7)	-0.5 (-2.2–1.4)
Symptoms	86	66.4 (37.5–84.3)	61.4 (37.9–74.3)	-2.0 (-6.2–1.6)
Activity	86	61.1 (35.5–86.6)	69.6 (36.2–92.5)	0.2 (-1.3–2.5)
Impacts	86	39.3 (17.7–54.5)	34.0 (16.2–54.0)	-0.1 (-2.4–1.9)
SF36				
Physical	86	39.7 (28.8–47.6)	34.6 (29.1–47.6)	-0.4 (-2.2–1.1)
Mental	86	52.3 (42.6–57.8)	55.0 (46.7–59.3)	0.5 (-1.1–2.3)

Data are presented as median (interquartile range), unless otherwise stated. FEV_1: forced expiratory volume in one second; % pred: % predicted; VC: vital capacity; RV: residual volume; TLC: total lung capacity; $T_{L,CO}$: gas transfer of the lung for carbon monoxide; V_A: alveolar volume; SGRQ: St George's Respiratory Questionnaire; SF36: Short-Form 36.

Linear regression of changes in lung function

Linear regression showed that bronchodilator reversibility and lower BMI at baseline were both independently associated with a greater decline in FEV1 (% pred) and together accounted for 14% of the overall variability in the decline. An increasing number of exacerbations was the only independent factor associated with a greater decline in $T_{L,CO}$ (% pred), but accounted for only 5% of the variability in this decline.

DISCUSSION

The current study documents for the first time the nature, frequency, seasonal variability and incidence of acute exacerbations in AATD. It has been demonstrated that exacerbations occur commonly in patients with AATD and a third of the patients with exacerbations $\geqslant 3$ episodes per year (18% of the total group). The average number of exacerbations for the whole group is similar to that seen in non-AATD COPD in general [2]. The presence and frequency of exacerbations remain consistent from year to year and, although exacerbations occurred throughout the year, nearly a third occurred in December and January. The median length of symptoms in these patients is 14 days, which, despite being based largely on patient recall, is similar to the duration determined prospectively by diary cards in an earlier subgroup of AATD patients [19], and is greater than the 7 days seen in usual COPD using similar documentation [20]. Taken together, these data suggest that AATD alone does not predispose to exacerbations, but may influence their resolution.

When the current study started in 1996 there was no consensus about the definition of an exacerbation, which has subsequently been agreed to include a change in the patient's regular medication in 2000 [21] and, hence, such data was not formally collected. Nevertheless, the overall frequency is similar to that seen in COPD in general, when this more rigorous definition is applied, suggesting that the data are equally valid. The present authors also acknowledged the potential for recall bias when the patients were asked about details of their exacerbations during the previous year. However, the data is consistent with that obtained in the authors' more limited study where the data was validated with diary cards and examination of primary care records [19]. The current authors' feel that the present results are representative of the number and nature of exacerbations in AATD.

The patients included in the study were all nonsmokers or exsmokers and so this data cannot be extrapolated to patients with AATD who continue to smoke. The population used was an unselected group of AATD patients and, thus, the patients showed a range of lung function from normal to severely impaired.

Chronic mucus hypersecretion has been shown to be associated with an increased likelihood of exacerbations in usual COPD [22] and in AATD [10]. In the current study, 42% of the patients had chronic bronchitis and these patients showed an increased frequency of exacerbations, confirming previous findings [10].

Although index patients had more exacerbations than non-index patients in the univariate analysis, index status was not independently related to exacerbations in the multivariate analysis. Index patients had a greater smoking history and a lower baseline FEV1 and patients with more severe airflow obstruction had more frequent exacerbations, which probably accounts for the initial association with index status. In addition, increased air trapping (as measured by RV) was also shown to be associated with exacerbations. The reason for this is unknown but increased air trapping would increase the work of breathing and may, therefore, lead to a greater awareness of slight pathophysiological changes that would increase this work further and be reflected in the awareness of increased breathlessness. Alternatively, the exacerbations themselves may damage the small airways leading to an increase in air trapping. At present, it remains unknown whether this is a cause or effect, but the observed relationship between FEV1 decline and exacerbation frequency in usual COPD [23] is more supportive of a direct effect in those patients. However, it remains unknown why this is not reflected in a change in FEV1 in AATD.

Bronchodilator reversibility was also associated with exacerbations and this may reflect a change in the reversible component of airways function during such episodes. In the current study, the immediate effect of an exacerbation on spirometry and reversibility was not investigated because of patient distance from the centre, but other studies have shown some correlation between symptoms of dyspnoea and a temporary reduction in peak flow measurements [20].

Exacerbations were also more frequent in patients using an inhaled steroid. However, the current study was not designed as an interventional study and this observation may reflect the practice of prescribing inhaled steroids more often in patients with frequent exacerbations or in those with lower lung function.

Exacerbations were shown to have an influence on health status scores, which supports data obtained by other groups in usual COPD [2, 24]. For the SGRQ symptom score, this reflects the fact that two of the component questions ask about ''the number and length of attacks of chest trouble''. However, worse health status in the patients with frequent exacerbations was also reflected in the other individual components and total score of the SGRQ as well as the components of the SF36. This association was not due to a difference in lung function alone as exacerbations were found to have an additional independent effect on health status scores using regression analysis. In addition, other factors, such as increasing age, chronic bronchitis, and increase in pack-yr smoking history as well as reduced FEV1, were all shown to have independent effects on health status scores irrespective of exacerbations. This confirms that QoL, as measured by these questionnaires, is affected by many factors other than physiological impairment and that improvement in health status measures is potentially achievable by using several diverse therapeutic strategies. The suggestion that augmentation therapy reduces exacerbations [6] may, therefore, be an important therapeutic aim in patients with AATD.

During previous work [5], the authors' group documented improvements in SGRQ symptom score in a small number of patients attending for review at their specialist clinic over 2 yrs. The current study shows that this improvement is progressive and is sustained in a larger group of patients over

a longer period of time and reflects a change that is recognisable by the patients. The improvement was greater in patients with <3 exacerbations per year.

Of more importance, the overall health status did not decline despite major changes in lung function (mean FEV1 decline of 171 mL over the 3 yrs). MIRAVITLLES *et al*. [25] have also shown an improvement in SGRQ symptom score in a cohort of non-AATD COPD patients despite worsening activity, although this was not a progressive improvement as shown in the current study. Other data in usual COPD shows a decline in health status over time with an increase in SGRQ total score of 9.6 points over 3 yrs when the FEV1 falls by 177 mL although a lesser change of 6.0 points occurs in patients on inhaled steroids with a mean FEV1 decline of 150 mL [26, 27]. Since the patients had a similar decline in FEV1 to that seen in the above studies, it would be expected that the SGRQ should also change by at least this amount. Recently STOLK *et al*. [28] have demonstrated a worsening of SGRQ score in 22 patients with AATD over 30 months with a mean change of 6.5 units (-2.9–17.5). The lack of significant change in overall health status in the current cohort, despite documented deterioration in lung function and activity, may reflect as yet undefined benefits of the specialist clinic in which patients are seen on an annual basis in the UK. Inhaled steroid treatment was not altered significantly in these patients over the study period, although other therapeutic measures, such as the use of long-acting β-agonists, an altered management strategy for the treatment of infections and improved patient education may have played a role in the maintenance of health status over the 3-yr period.

It can be confirmed that lung physiology measurements deteriorate in these patients over time. The decline in spirometric values in this study is not related to the frequency of exacerbations in the whole group or in subgroups according to airflow obstruction. This is contrary to the findings of DONALDSON *et al*. [23] in usual COPD. However, other workers have suggested that only smokers are susceptible to an influence of exacerbations on FEV1 decline [29] and the patients in the present 3-yr study were all ex-smokers or nonsmokers. It is also possible that exacerbations have a less clear deleterious effect on FEV1 in AATD patients than in usual COPD patients, due to the increased ongoing inflammation in the stable state. The FEV1 decline was, however, associated with greater bronchodilator reversibility at baseline as has been seen previously [3, 5], and this may be due to an increase in airway inflammation contributing to both airways hyperreactivity and subsequent structural changes in the airways.

The decline in $T_{L,CO}$ was associated with the number of exacerbations. The proposed pathogenic mechanism for the development of emphysema and decreased gas transfer in AATD is related to an increased neutrophilic elastase burden along with reduced protection due to low α_1-antitrypsin levels. An increase in elastase challenge is seen during periods of exacerbations especially in AATD [19], but this is only a feature of purulent exacerbations. In this study, the majority of exacerbations were classified as type 1, which, by definition, includes purulent sputum as a feature. Thus, increased elastase activity should be present in most of these episodes and may lead to tissue destruction and, hence, to a reduction in the gas transfer. However, it should be noted that such episodes were not related to the decline in $T_{L,CO}/V_A$. The $T_{L,CO}$ reflects not only alveolar gas exchange but also regional gas distribution, which will be influenced by small airways damage. Exacerbations are more likely to be related to infection and inflammation in the airways than in the alveoli. Thus, such episodes may have more effect on the small airways and any subsequent structural change would lead to altered distribution of ventilation, thereby reducing the $T_{L,CO}$ but not $T_{L,CO}/V_A$.

α_1-Antitrypsin augmentation therapy may lessen the decline in lung function in α_1-antitrypsin deficiency, as has been suggested by WENCHER *et al*. [30]. LIEBERMAN [6] has hypothesised that augmentation therapy may also reduce the frequency and severity of infections in α_1-antitrypsin deficiency on the basis of patient opinion on the effect of their treatment. Prospective controlled studies are therefore needed to further investigate these hypotheses and future trials of antiprotease replacement should include exacerbations as an important outcome measure. If a reduction in exacerbations can be achieved with augmentation therapy, the current data suggests it should also influence quality of life and decline in lung function, although not necessarily the decline in forced expiratory volume in one second. The current study provides a firm basis upon which to design, power and implement such trials.

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