Long-term treatment of α_1-antitrypsin deficiency-related pulmonary emphysema with human α_1-antitrypsin

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ABSTRACT: α_1-antitrypsin (α_1-AT) deficiency is a genetic disorder characterized by low serum levels of α_1-AT and a high risk of pulmonary emphysema at a young age. The resulting surplus of proteases, mainly of neutrophil elastase, can be balanced by *i.v.* augmentation with α_1-AT. However, it is not clear if affected patients benefit from long-term augmentation therapy and no long-term safety data are available.
We examined 443 patients with severe α_1-AT deficiency and pulmonary emphysema receiving weekly *i.v.* infusions of 60 mg·kg body weight^{-1} α_1-AT in addition to their regular medication. The progression of the disease was assessed by repeated lung function measurements, particularly the decline in forced expiratory volume in one second (ΔFEV1).
Four hundred and forty three patients with α_1-AT deficiency tolerated augmentation therapy well with few adverse reactions. The ΔFEV1 in 287 patients with available follow-up data was 57.1 ± 31.1 mL·yr^{-1}. Stratified for baseline FEV1, the decline was 35.6 ± 21.3 mL in the 108 patients with an initial FEV1 <30% and 64.0 ± 26.4 mL in the 164 with FEV1 30–65% of predicted normal (p=0.0008). The remaining 15 patients had an initial FEV1 >65% pred.
Long-term treatment with *i.v.* α_1-antitrypsin in patients with severe α_1-antitrypsin deficiency is feasible and safe. The decline in forced expiratory volume in one second is related to the initial forced expiratory volume in one second as in α_1-antitrypsin deficient patients not receiving augmentation therapy.
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α_1-antitrypsin (α_1-AT) is one of the most important human protease inhibitors, providing more than 90% of the antiproteolytic capacity of the lower respiratory tract [1]. Mutation of the α_1-AT gene is one of the most frequently inherited abnormalities in humans. The most common mutation of the protease inhibitor is the Z variant, which is carried by 1 in 50 people of Northern European descent [2, 3]. Homozygocity for the Z allele is associated with α_1-AT plasma levels in only 15% of normal subjects [4]. Subjects with this defect have an increased risk of pulmonary and liver disease [5]. Pulmonary disease is thought to be due to an imbalance of proteases and antiproteases. Surplus proteases result in an accelerated degradation of lung connective tissue. Many affected individuals suffer from early onset pulmonary emphysema that becomes symptomatic in the third or fourth decade [6]. It is therefore rational to augment α_1-AT plasma levels to reduce the protease burden and to increase the protective antiprotease shield of the lower respiratory tract.

Since 1989 *i.v.* therapy with human α_1-AT has been available in several countries. For short-term *i.v.* therapy with human plasma-derived α_1-AT, safety and biochemical efficacy was demonstrated [7–9]. However, although several thousand patients receive augmentation therapy on an

regular basis, data on safety and tolerability of long-term treatment with α_1-AT is only anecdotal [10, 11]. Also, it is not clear if biochemical efficacy also results in a decelerated course of pulmonary disease. Parameters correlating best with the clinical outcome of patients with chronic obstructive pulmonary disease are the decline in forced expiratory volume in one second (ΔFEV1) and mortality. Because of the slow progression of the disease, the high intra- and interindividual variations of lung function, and the small number of identified patients with α_1-AT deficiency, investigators have found it difficult to conduct a controlled study to prove clinical efficacy [12] of α_1-AT replacement therapy.

The aim of this study was to prospectively evaluate results of long-term *i.v.* α_1-AT augmentation in patients with pulmonary emphysema secondary to hereditary α_1-AT deficiency, and particularly to monitor adverse reactions and changes in lung function.

Methods

Patients

Patients with proven α_1-AT deficiency and pulmonary emphysema were admitted to this multicentre, surveillance

study. Recruitment started in February 1989 and the closing date was the December 31, 1995. A total of 443 patients from 25 pulmonary centres throughout Germany were consecutively included. Patients came to the attention of the participating pulmonary hospitals or were referred by a pulmonary specialist on account of pulmonary symptoms (dyspnoea on exertion, occasional wheezing and coughing, and frequent infections of the respiratory tract).

Pulmonary emphysema is defined by pathological criteria and recent studies show that computed tomography (CT) scans have a better correlation with pathological changes than FEV1 [13]. All of our patients had a CT scan of the thorax before or shortly after entering the study. CT scans were evaluated individually by an expert radiologist and investigator of the respective centre. All patients showed signs of pulmonary emphysema on CT scans. The extent of emphysema in these patients is not available, some may have had only minor emphysema. Only preliminary data on the follow-up of emphysema with CT scan are available [14]. These show that regular measurements of mean attenuation values may be a valuable tool to assess the progress of emphysema in patients with α_1-AT deficiency. In the quoted study, the data are from one centre using one specific CT scanner. However, the current study involves a large number of centres using different scanners. In 1987, when this multicentre surveillance study was set up, a standardization of the various CT scanners in use over a period of almost 10 yrs was not feasible so that no follow-up data for the entire group are available.

To confirm the α_1-AT deficiency, the phenotype was usually determined by isoelectric focusing before the first treatment with α_1-AT and reported to the study co-ordinator. Patients with serum levels of <50 mg·dL^{-1} measured by nephelometry or <80 mg·dL^{-1} measured by radial immunodiffusion were considered for augmentation therapy regardless of phenotype. These values are equivalent to serum levels of 35% of normal or 11 μmol by the National Institutes of Health (NIH) standard [15], which are assumed to provide a protective level at which the development of pulmonary emphysema is unlikely [16]. Patients older than 18 yrs with severe α_1-AT deficiency were included if lung function was impaired with FEV1 <65% predicted, or an annual decline of FEV1 of >120 mL was observed. Patients were required to stop smoking in order to participate in the study. They must have stopped for at least 3 months prior to the first infusion. Nonsmokers had never smoked. Exsmokers had stopped prior to entering the study. A laboratory control to verify smoking status was not part of the protocol.

All patients received weekly *i.v.* augmentation therapy with human plasma-derived α_1-AT (Prolastin® HS, Bayer, Leverkusen, Germany). The dose was 60 mg·kg body weight^{-1} and the infusion was usually administered by the patient's general practitioner, sometimes at the study centre or in a hospital. Most patients routinely received bronchodilator and anti-inflammatory drugs. Co-medication was not affected by augmentation therapy. Exclusion criteria were known hypersensitivity to blood products or selective immunoglobulin (Ig)A deficiency, pregnancy and signs of right heart failure. Patients who underwent lung or liver transplantation, lung reduction surgery or bullectomy were excluded from further analysis. The patients who failed to return to the study centre were con-

tacted, to motivate them to continue follow-up visits. If augmentation therapy had to be discontinued or the recommended treatment interval was changed for reasons unrelated to the study, patients were excluded from further analysis and data censored from that point.

Lung function measurements were done before the beginning of augmentation therapy, 1 week after the beginning of the study, after 3 and 6 months and then every 6 months at the study centre. A flow-volume loop and whole body plethysmography measurements were carried out before and after bronchodilation with two puffs of salbutamol of 100 μg each. In each case the best of three trials was used for further analysis. The measurements were performed in accordance with European recommendations by specially trained personnel. All participating centres have an internal quality-control assessment for pulmonary function tests. The detailed analysis of all FEV1 data show low intra-individual variability, which supports the quality of pulmonary function tests. Predicted values of the measured variables were calculated according to European reference equations (European Coal and Steel Community) [17]. The values for arterial oxygen tension (Pa,O$_2$) were calculated according to the equation from COTES [18].

Statistical analysis

The main single parameter to monitor the progress of emphysema was the ΔFEV1 per year. Since smoking was identified as one of the major risk factors in the development of emphysema in patients with α_1-AT deficiency, patients were grouped according to their smoking status. To eliminate the effect of reversible airway obstruction, this analysis was made for postbronchodilator FEV1 only. For any given patient, a minimum of one "baseline" and two follow-up postbronchodilator FEV1 measurements were required to be included into further analysis. "Baseline" was defined as the earliest available postbronchodilator FEV1 measurement out of the assessments immediately before, at the beginning of, or 3 months after the beginning of augmentation therapy. Thus, every patient included received a minimum of 1 yr of augmentation therapy. To calculate the slope of decline of FEV1, a mixed-effect analysis of variance (ANOVA) model was used. The individual slope and intercept of the ΔFEV1 were included as random effects and a set of relevant variables (common slope, smoking status, age, sex, baseline class of FEV1, interaction terms between these variables and ΔFEV1 if statistically significant) were considered as fixed. Since, due to stability reasons, the inclusion of FEV1 as a continuous covariate into the model was not possible, patients were divided into three baseline classes (FEV1 <30% pred, 30–65% pred, and >65% pred) for this statistical analysis. The restricted maximum likelihood method was used in estimating the model and an unstructured covariance matrix for random factors was specified and fitted within the model [19]. Each patient's individual ΔFEV1 was calculated by superimposing the solution for the fixed effects upon the best linear unbiased prediction as a solution for the random effects. The model fit was performed using the PROC MIXED module of the SAS software (SAS-Institute 1992, Cary, NC, USA). Effects of "informative right

censoring" due to "attrition" (death, loss to follow-up, lung transplant) were not taken into consideration because of the very small incidence of such events. Univariate methods were used to calculate the descriptive statistics for the predicted $\Delta FEV1$ for each patient.

Results

Demographic data at baseline

Four hundred and forty three patients (151 female and 292 male) with severe α_1-AT deficiency and pulmonary emphysema received weekly *i.v.* augmentation therapy with human α_1-AT. The mean age was 47±9 yrs. The age distribution was similar for males and for females and in both cases slightly skewed to the right. Eighty per cent of the patients were exsmokers and only 20% had never smoked. There was no difference in treatment duration and number of visits between these groups but never-smokers began treatment approximately 5 yrs later than exsmokers and the difference in the age at the beginning of treatment was statistically significant (table 1). The percentage of males in the group of exsmokers was significantly higher whereas in the nonsmokers the ratio of males and females was equal (table 1). There were no significant differences in the baseline postbronchodilator FEV1 and FEV1 % pred in exsmokers and never-smokers. For subgroups with different degrees of pulmonary function impairment the age was not significantly different (FEV1 ≤30% pred, mean age 45.5±8.2 yrs; FEV1 >30 and ≤ 65% pred, mean age 47.0±8.7 yrs, p=NS).

All patients had signs of moderate to severe pulmonary emphysema with markedly reduced FEV1, well-preserved vital capacity (84.9±20.6% pred), and signs of hyperinflation with a residual volume of 262.1±75.8% pred. Most patients had moderate to severe signs of irreversible bronchoconstriction with a mean airway resistance of 4.54± 2.31 $cmH_2O \cdot L \cdot s^{-1}$ (normal 0.5–3.0).

Of the 443 patients, 394 presented with a PiZZ phenotype and 31 patients had a PiSZ phenotype, with both reduced plasma levels of α_1-AT and pulmonary emphysema. Six patients were identified as PiZNull and three as PiFZ; nine patients either had other phenotypes or their phenotype was not known. Comparison of baseline data did not show any significant differences between PiZZ and PiSZ phenotypes.

Safety of treatment with α_1-AT

All 443 patients included in this drug surveillance study received weekly *i.v.* augmentation therapy with 60 mg·kg body weight^{-1} human α_1-AT (Prolastin® HS) and showed a marked increase of α_1-AT serum levels after the infusion. The baseline values of α_1-AT were not different for exsmokers and nonsmokers (49.5±23.9 *versus* 57.3±31.2 mg·dL^{-1} for radioimmunodiffusion, and 33.6±22.1 *versus* 30.4±15.1 mg·dL^{-1} for nephelometry, respectively, p=NS).

After the beginning of augmentation therapy, plasma levels were consistently above the presumed protective threshold of 80 mg·dL^{-1} [9] with median trough levels of 95 mg·dL^{-1}.

Between February 1989 and December 1995, a total of approximately 58,000 infusions were administered to 443 patients. In general, therapy was well tolerated. One hundred and twenty four adverse reactions were reported in 65 patients. In the majority of the patients the observed adverse reactions were typical reactions noted in *i.v.* infusions of proteins, *i.e.* fever/chills in 17, urticaria in 18, nausea and vomiting in 21 and fatigue in seven patients. A total of 19 adverse reactions occurred in the 17 patients mentioning increased dyspnoea. Three patients terminated treatment with α_1-AT permanently because of repeated episodes of fever and chills immediately after infusions of α_1-AT from different batches on more than one occasion. Five severe adverse reactions requiring medical intervention or hospitalization were observed. In four patients, anaphylactic reactions occurred and one patient suffered worsened congestive heart failure and concomitant respiratory failure. In all cases a complete recovery was obtained. No death and no viral transmission, especially human immunodeficiency virus (HIV) or hepatitis, directly related to α_1-AT augmentation therapy were observed during the study period.

Thirty seven patients continued treatment but were lost to further follow-up for reasons unrelated to the therapy. Thirteen patients underwent lung transplantation (LTX) for terminal emphysema due to α_1-AT deficiency and were not included in further analysis. Fifty nine patients died during the study, and in the majority of cases the cause of death was associated with the underlying pulmonary disease.

Longitudinal data on $\Delta FEV1$

In 287 patients (187 male, 100 female, mean age 46±9 yrs) a minimum of baseline and two postbronchodilator FEV1 measurements were available for analysis of longitudinal changes of lung function data. The mean follow-up time was 37.8±18.9 months and the mean number of lung function measurements available for one patient was 6.2±2.7. The mean decline of FEV1 was 57.1±31.1 mL·yr^{-1} for the entire group, and there were no differences for exsmokers and nonsmokers (55.9±31.3 and 62.1±28.9 mL·yr^{-1}, respectively; p=0.56). Again, patients showed markedly

Table 1. – Demographic details of the patient sample at enrolment, stratified for smoking status

	Exsmokers (n=356)	Nonsmokers (n=87)
Age yrs	45.4±7.7	51.2±9.7***
Sex males/females	248/108	44/43***
Phenotypes		
PiZZ	322	72
PiSZ	20	11
Other or unknown	14	4
Treatment duration months	29.2 (3.4–79.7)	23.4 (3.1–82.8)
Visits after baseline n	3.9 (0–12)	3.4 (0–12)
Baseline FEV1 L·s^{-1}	1.32±0.62	1.38±0.67
Baseline FEV1 % pred	35.5±14.8	42.2±18.2

Data are presented as absolute number, mean±SD, or mean with range in parenthesis. FEV1: forced expiratory volume in one second; % pred: percentage of predicted values. ***: p<0.001.

Table 2. – Baseline lung function values after bronchodilation for 287 patients with available follow-up data

Parameter		Value	% predicted
FEV1	L·s⁻¹	1.33±0.63	36.3±15.2
FVC	L	3.6±1.1	84.9±20.6
FEV1/FVC	%	37.0±11.2	47±14
TLC	L	8.8±1.9	136.2±22.4
RV	L	5.2±1.7	262.1±75.8
P_{O_2}	kPa	9.2±1.2	9.9±1.3

Data are presented as mean±SD. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; P_{O_2}: partial oxygen pressure. 1 kPa=7.52 mmHg.

reduced FEV1, signs of hyperinflation, and well-preserved vital capacity (table 2). Importantly, distribution of age, gender, smoking status as well as baseline lung function of this subgroup was similar to the whole study population as well as the 156 patients without available follow-up data (p>0.1, all comparisons). Stratified for baseline FEV1, the decline was 35.6±21.3 mL in patients with an initial FEV1 <30% (n=108) (fig. 1a) (median 35.3 mL, 95% confidence interval (CI) 0.2–74.5 mL) and 64.0±26.4 mL in those with FEV1 30–65% (n=164) (fig. 1b) (median 64.3 mL, 95% CI 24.4–107.3 mL) (p=0.0008) (table 3). The remaining 15 patients had FEV1 values of >65% pred. The ΔFEV1 for these patients was 124.0±46.5 mL·yr⁻¹. This rapid decline in ΔFEV1 reflects the inclusion criteria of FEV1 <65% pred or ΔFEV1 >120 mL·yr⁻¹. Due to the small number of patients in this subgroup, a detailed statistical analysis was not possible.
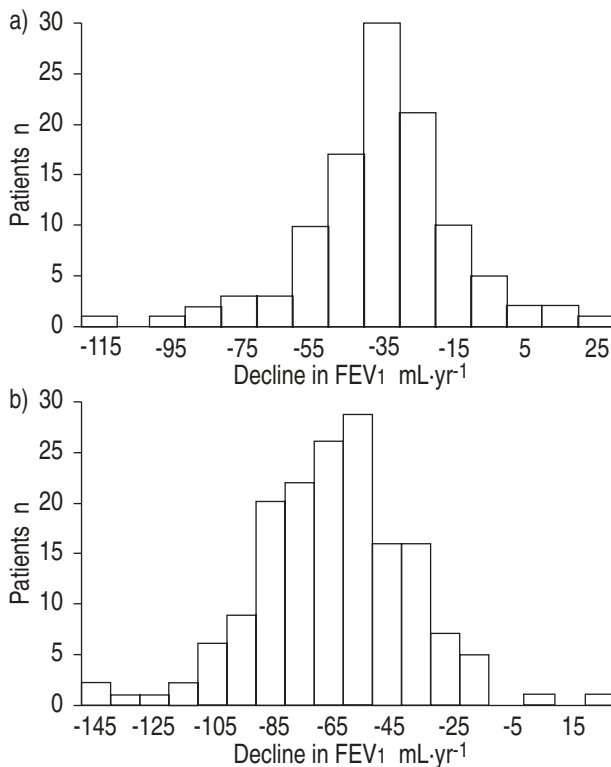

Fig. 1. – Rate of changes in forced expiratory volume in one second (FEV1): a) for 108 subjects with a baseline FEV1 <30% predicted and b) for 168 subjects with a baseline FEV1 between 30–65% pred.

Table 3. – Relation between the severity of functional impairment and yearly decline in FEV1

	FEV1 δ30% pred (n=108)	FEV1 30–65% pred (n=164)
Age yrs	45.5±8.2	47.0±8.7
FEV1 % pred	23.6±4.1	42.1±8.3
Decline in FEV1 mL·yr⁻¹	35.6±21.3	64.0±26.3***

Data are presented as mean±SD. FEV1: forced expiratory volume in one second. ***: p=0.0008, analysis of variance test.

Discussion

α_1-AT deficiency is one of the most frequent inherited diseases in Caucasians; it often results in premature pulmonary emphysema between the third and fourth decades. The pathogenesis of emphysema in α_1-AT deficiency is thought to be due to an imbalance between proteases and antiproteases resulting in proteolytic destruction of lung tissue. The only specific therapy available is *i.v.* augmentation therapy with human α_1-AT by which levels in plasma and epithelial lining fluid (ELF) can be increased to a presumably protective threshold [8]. However, while biochemical efficacy was demonstrated [9], no data on long-term safety and efficacy of *i.v.* α_1-AT augmentation therapy have yet been available.

Feasibility and safety of α_1-AT replacement therapy

This study shows that weekly *i.v.* augmentation therapy with human α_1-AT is feasible and can be used safely in the long-term treatment of patients with severe pulmonary emphysema due to α_1-AT deficiency. Despite its inconvenience, it is well accepted by patients, even after many years of treatment. Even those patients who failed to return to their study centre for further visits continued *i.v.* augmentation therapy, to our knowledge. The number and severity of adverse reactions after α_1-AT application is low, an important prerequisite for long-term treatment.

α_1-AT augmentation therapy in the USA and in Germany is only approved for weekly *i.v.* infusions. However, weekly *i.v.* infusions over a period of many years is not a very convenient form of therapy. To reduce the number of infusions, one group of investigators have used monthly *i.v.* infusions to augment α_1-AT levels in patients with α_1-AT deficiency. The biochemical efficacy of this treatment was shown by elevated α_1-AT levels in serum and ELF 30 min after infusion. In monthly replacement therapy of nine patients, serum levels remained >80 mg·dL⁻¹ for an average of 21 days after the first infusion and 25 days after 12 months of therapy. ELF levels of α_1-AT of four patients were consistently above the assumed protective threshold of 1.3 µmol after the second month of observation [20]. However, the efficacy of monthly augmentation therapy was questioned by CAMMARATA *et al.* [21] who repeatedly observed serum trough levels below 80 mg·dL⁻¹ in all five patients treated with a monthly regimen. Also, it has recently been demonstrated that in 40% of the patients the infusion of 120 mg·kg⁻¹ body weight biweekly, could not maintain through levels above 80 mg·dL⁻¹ for more than 10 days [22].

Another anticipated problem of monthly augmentation therapy is the fourfold increase of protein infused which may lead to an increased cardiac stress. At least in some of our patients the reported increased dyspnoea associated with the α_1-AT infusion is due to the relatively high protein load and we assume that the number of adverse reactions due to this mechanism would increase in monthly augmentation therapy. Because of this and since α_1-AT augmentation therapy in the USA and in Germany is only approved for weekly infusions, the weekly regimen was part of the protocol and compliance was required.

As in the previously published results of a German registry, the number of males included in the study was about twice as high as the number of females [23]. At first glance this is surprising since α_1-AT deficiency is an autosomal codominantly inherited disease and the expected gene distribution is equal in males and females. Further analysis shows that a male predominance is only found for exsmokers whereas in the never-smokers the male/female ratio is equal. The overall predominance of males in this study therefore reflects most probably the higher percentage of smoking males in the German population.

Rationale and efficacy of α_1-AT replacement therapy

Taking into account the poor prognosis of patients with severe pulmonary emphysema due to α_1-AT deficiency and the preliminary, yet convincing, data for α_1-AT replacement therapy [7, 24–27], the study group felt that for ethical reasons it was not feasible to subject patients to a long-term *i.v.* placebo (*e.g.* albumin) treatment and deny a possibly beneficial treatment.

Since our study is not a placebo-controlled trial, it is thus impossible to directly compare our data with untreated or placebo-treated patients from the same population, or prove efficacy of therapy with α_1-AT on the basis of the data collected. However, our data favourably compare to all reported data related to the decline of $FEV1$ over time in untreated index cases with pulmonary emphysema and α_1-AT deficiency. The yearly $\Delta FEV1$ in patients treated with *i.v.* α_1-AT was only 57.1 ± 31.1 mL in our study. This is approximately half of the rate of decline previously reported for untreated index cases [24–27]. In a recent paper the Danish group found a decline in $FEV1$ of 59.1 mL in 74 index cases who had ceased smoking [26]. However, in this subgroup no information on the initial $FEV1$, age, sex, number of measurements and time of follow-up was available. Re-analysis of this group that now comprised 98 patients 2 yrs later resulted in an increase in $\Delta FEV1$ from 59 to 74.5 mL [28].

The group of patients in which the progress of emphysema is best described by the $\Delta FEV1$ is probably that with $FEV1$ between 30–65% pred. A combined USA and Swedish study particularly analysed the $\Delta FEV1$ of patients with an $FEV1$ between 30–65% pred [27]. Comparing the results of the patients with $FEV1$ 30–65% pred only with the data from the National Heart, Lung and Blood Institutes (NHLBI) workshop of nonaugmented patients [27] most of the known confounding factors are similar: the age was 45 ± 9 for 30 USA and 47 ± 8 yrs for 41 Swedish individuals compared to 47.0 ± 8.7 yrs in 164 of our patients. The mean initial $FEV1$ % pred was 41.9 ± 10.7 and 43.3 ± 9.6% compared to 42.1 ± 8.3%. Some nonindex cases were included into the NHLBI analysis and the percent-

age of index cases is not reported. Also, there were 17% of current smokers in the USA group and 24% in the Swedish group, respectively, which may have caused a bias towards a higher $\Delta FEV1$. However, the $\Delta FEV1$ found in the NHLBI study was 111 ± 102 and 104 ± 94 mL·yr^{-1} compared to 64.0 ± 24.4 mL·yr^{-1} in our treated group. Since this is not a controlled trial this comparison does not prove efficacy of augmentation therapy but it warrants further investigation.

Not surprisingly, the $\Delta FEV1$ is a function of the baseline value (table 3), and patients with well-preserved $FEV1$ lose more millilitres per year than patients with advanced emphysema. This is also due to "right censoring" indicating that patients with a more rapid decline would have a higher likelihood of death or receiving a lung transplant.

Even though there was no statistically significant difference between exsmokers and nonsmokers regarding $FEV1$ % pred, the difference between groups was appreciable (35.5 ± 14.8 *versus* 42.2 ± 18.2%). This may be due to the fact that both smokers and physicians attribute coughing, wheezing, and increasing dyspnoea to their smoking habit rather than to another underlying disease. This may be one cause for the late diagnosis of α_1-AT deficiency.

This is not a double-blind placebo-controlled trial, and the data presented here cannot prove the efficacy of this treatment. As α_1-AT deficiency is a rare, slowly progressive disease, a great number of patients and long-term follow-up are required. These are still the major impediments to a placebo-controlled trial [12]. Clearly, further studies are needed to support the findings reported here. One way to prove efficacy would be to compare our data with a well-matched group of patients not receiving augmentation therapy. This analysis has just been published and showed a statistically significant difference between treated and untreated individuals with $FEV1$ 30–65% pred [28]. Also, if a reproducible surrogate marker for the progression of pulmonary emphysema other than $FEV1$, whether biochemical or radiological or other, could be identified, the number of patients and the period of observation needed for a double-blind, placebo-controlled trial could be greatly reduced and thus rendered possible.

In conclusion, long-term treatment with *i.v.* α_1-antitrypsin is feasible and safe. To prove efficacy of this therapy in patients with severe α_1-antitrypsin deficiency, a controlled study would be desirable [29].

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