Longitudinal Follow-up of Patients With α_1-Protease Inhibitor Deficiency Before and During Therapy With IV α_1-Protease Inhibitor*

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Background: **The efficacy of IV augmentation therapy with human α_1-protease inhibitor (α_1-Pi) in patients with severe α_1-Pi deficiency is still under debate.**
Study objectives: **To evaluate the progression of emphysema in patients with α_1-Pi deficiency before and during a period in which they received treatment with α_1-Pi.**
Design: **Multicenter, retrospective cohort study.**
Setting: **Outpatient clinics of 26 university clinics and pulmonary hospitals.**
Patients: **Ninety-six patients with severe α_1-Pi deficiency receiving weekly augmentation therapy with human α_1-Pi, 60 mg/kg of body weight, had a minimum of two lung function measurements before and two lung function measurements after augmentation therapy was started. Lung function data were followed up for a minimum of 12 months both before and during treatment (mean, 47.5 months and 50.2 months, respectively).**
Measurements and results: **Patients were grouped according to the severity of their lung function impairment. The change in FEV_1 was compared during nontreatment and treatment periods. In the whole group, the decline in FEV_1 was significantly lower during the treatment period (49.2 mL/yr vs 34.2 mL/yr, $p = 0.019$). In patients with $FEV_1 > 65\%$, IV α_1-Pi treatment reduced the decline in FEV_1 by 73.6 mL/yr ($p = 0.045$). Seven individuals had a rapid decline of FEV_1 before treatment, and the loss in FEV_1 could be reduced from 256 mL/yr to 53 mL/yr ($p = 0.001$).**
Conclusion: **Some patients with severe α_1-Pi deficiency and well-preserved lung function show a rapid decline in FEV_1. These patients profit from weekly IV therapy with human α_1-Pi and have less rapid decline if treated. Early detection of patients at risk and early start of augmentation therapy may prevent accelerated loss of lung tissue.** ***(CHEST 2001; 119:737–744)***

Key words: α_1-antitrypsin; α_1-antitrypsin deficiency; augmentation therapy; emphysema; lung function; smoking

Abbreviations: α_1-Pi = α_1-protease inhibitor; ΔFEV_1 = change in FEV_1 per year; WATL = Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen

Shortly after α_1-protease inhibitor (α_1-Pi) deficiency was first described by Laurell and Eriksson[1] in 1963, the function of the protein was investigated in detail. It was discovered that it is not only an effective inhibitor of trypsin (hence the synonym *α_1-antitrypsin*) but in fact the major antiprotease in the airways. α_1-Pi protects the airways from destruction by surplus endogenous or exogenous proteases.[2]

For editorial comment see page 676

While the protease-antiprotease hypothesis gained rapid acceptance not only as a model for the development of emphysema in patients with severe α_1-Pi deficiency but also as the underlying mechanism leading to smoker's emphysema, the correction of the deficiency by IV augmentation therapy with human α_1-Pi is still under debate. This controversy is because of the lack of placebo-controlled clinical trials that prove the efficacy of augmentation therapy.[3] Reasons for the lack of these studies are manifold: (1) α_1-Pi deficiency is a rare disease, and only 5

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to 10% of the estimated affected patients are identified; (2) the lung disease develops slowly over many years; and (3) the tools to monitor the progression of emphysema are too crude to pick up minor deterioration of emphysema. When human α_1-Pi became available for augmentation therapy in 1987, the obstacles of a two-armed, placebo-controlled trial including some 300 patients over at least 3 years could not be overcome, and it was decided to treat patients on the basis of the biochemical evidence provided by the protease-antiprotease hypothesis.[4]

Twelve years later, conclusive placebo-controlled trials are still to be undertaken, but some evidence has accumulated to support the clinical efficacy of IV augmentation therapy. In a prospective study, we could show that this treatment is safe and that the decline in FEV_1 is slowed by IV α_1-Pi treatment compared to historical data.[5] Compared to a group of Danish patients with moderate emphysema who never received augmentation therapy, the decline in FEV_1 was significantly lower in the treated German patients.[6] These results were confirmed by a US study[7] that also demonstrated a reduced mortality rate for patients with moderately advanced emphysema. The results of the only placebo-controlled trial[8] conducted so far were published in 1999. The Danish-Dutch study group[8] included 28 patients in each arm and followed up patients for 3 to 5 years, performing lung function tests every 3 months, daily home spirometry, and annual CT of the thorax. Not surprisingly, the 3-month FEV_1 measurements did not indicate any significant differences between the placebo and treatment groups. Because of autocorrelation, a problem described in detail by Dirksen et al,[9] the daily FEV_1 measurements also failed to show a difference between the groups. The most promising data were the change of attenuation values on CT scan demonstrating a slower progress of emphysema in the treatment group that just fell short of demonstrating a statistical significant benefit of monthly augmentation therapy, mainly because of the small number of patients enrolled.

None of these studies analyzed data and compared the decline in FEV_1 of the same patients before and after the beginning of augmentation therapy. In such a longitudinal analysis, the patient serves as his own control and can eliminate some confounding factors inherent to the other studies.

The purpose of this study was to analyze the decline of FEV_1 in patients with severe α_1-Pi deficiency and different degrees of lung function impairment before and after the institution of augmentation therapy. The decline in FEV_1 was used as a marker for the progression of pulmonary emphysema, and it was investigated whether augmentation therapy could slow the development of pulmonary disease in these patients.

Materials and Methods

For this cohort study, we used one database that contained lung data before the institution of α_1-Pi therapy and a second database of a phase IV drug surveillance study.

Pretherapeutic Database

In 1987, the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenkrankungen (WATL) designed a central database to prospectively collect information on patients with severe α_1-Pi deficiency who were not receiving augmentation therapy at any time. A total of 26 centers contributed to this database; a total of 442 patients were included. Time intervals for lung function testing varied.

Therapeutic Database

After α_1-Pi purified from human blood (Prolastin HS; Bayer Vital; Leverkusen, Germany) was licensed for the treatment of severe α_1-Pi in Germany in 1989, regulatory authorities required a phase IV drug surveillance study. α_1-Pi is licensed in Germany for weekly infusion of 60 mg/kg of body weight only, and compliance to this protocol was required by all participating patients and physicians. Within this study demographic data, α_1-Pi levels and phenotypes as well as lung function data were collected prospectively at regular intervals (at the time of enrollment, after 3 months and 6 months, and then every 6 months). Inclusion criteria were as follows: (1) severe α_1-Pi deficiency with α_1-Pi serum levels $< 35\%$ of normal regardless of phenotype, (2) an FEV_1 of $< 65\%$ predicted or a decline in FEV_1 of > 120 mL/yr, and (3) nonsmokers or ex-smokers for at least 3 months at the time of enrollment. Exclusion criteria for augmentation therapy were known hypersensitivity against blood products, complete IgA deficiency, continued smoking, and history of right heart failure. Four hundred forty-three patients were included in this database, all of whom were index cases. Demographic data and the decline in FEV_1 in these 443 patients treated with IV human α_1-Pi were previously described in detail.[5] All available lung function data collected afterwards were added to the database and included in this comparison.

For the purpose of this analysis, *never-smokers* were patients who had smoked < 100 cigarettes in their lives, *ex-smokers* had stopped smoking before entering either of the two registries, and *smokers* were patients who smoked at least some time during the first part of the analysis, but had stopped a minimum of 3 months before they were started on IV α_1-Pi treatment.

Phenotypes were determined by isoelectric focusing as previously described by Fagerhol and Cox[10] and reported to the study coordinator. Spirometry was performed according to European Respiratory Society guidelines.[11]

Data from the WATL database contributed the pretherapeutic data. When patients were started on augmentation therapy, all following data were stored separately in the therapeutic database. This was the source for the data during augmentation therapy. Both databases, although only storing anonymous data, contained a mutual patient identifier so that those patients whose data were stored in both databases could be easily identified.

Patients with at least two lung function measurements before and two measurements after the institution of augmentation

therapy spaced at least 1 year apart were identified, and data from both databases were combined. Sufficient data in both databases were available on 97 patients. Ten patients received a lung transplant or underwent lung volume reduction surgery during the period reported, and their data were censored after their operation procedure. Because of this, in one patient, the follow-up time was < 1 year, so he did not meet the inclusion criteria stated above. In all, 96 patients with sufficient data were included in this analysis.

Statistical Analysis

Data are reported as mean ± SD. Continuous variables were tested using a two-sample *t* test. Dichotomous variables were analyzed using a χ^2 test; for ordinal values, we used a Wilcoxon signed-rank test.

To analyze the influence of augmentation therapy, the main outcome parameter was the change in FEV_1 per year (ΔFEV_1) before and after augmentation therapy. ΔFEV_1 was analyzed by mixed-effects modeling that included treatment (before vs during augmentation therapy) as fixed parameters and the individual patient with his FEV_1 measurements as the random variable. To analyze a possible treatment effect of augmentation therapy on the decline in FEV_1, double (for interindividual comparisons) and paired *t* tests (for intraindividual comparisons) were used. These tests were applied to the best linear unbiased predicted values for δFEV_1 as calculated from the mixed-effects model. The given values for ΔFEV_1 (mean and SDs) also refer to each individual patient's best linear unbiased predicted values.

Patients were grouped according to different degrees of functional impairment (FEV_1 < 30%, 30 to 65%, and > 65% of predicted normal, respectively), and these groupings were made either for the first available FEV_1 or the beginning of augmentation therapy. Particularly for patients with FEV_1 > 65% of predicted normal at (untreated) the start of observation, this also allowed us to identify patients who changed groups during the time they did not receive augmentation therapy (*rapid decliners*) and those who remained stable without augmentation therapy (*no decliners*). The comparison-wise type-1 error probability α was fixed to 0.05.

Results

A total of 96 patients (62 males and 34 females, p = 0.004) were available for analysis. The mean time of observation was 47.5 ± 28.1 months (range, 12.2 to 148.3 months) before augmentation therapy and 50.2 ± 30.2 months (range, 12 to 148.6 months) during the treatment period. The mean total observation time was 98.9 ± 36.6 months (range, 24.9 to 196.3 months). Twenty-eight patients had an observation period > 10 years.

The majority of patients had PiZ phenotypes, and the frequencies of the phenotypes did not differ between male and female patients. At the time when augmentation therapy was started, 12 patients had never smoked, 70 were ex-smokers, and 14 individuals had stopped smoking a minimum of 3 months before the beginning of therapy (hence, they were called smokers). A mean number of 4.9 FEV_1 measurements were available for analysis during this period, and 7.7 FEV_1 measurements were available during the treatment period. The absolute FEV_1 was significantly lower for female patients, but after adjustment for age, sex, and height (*ie*, the calculation of percent-of-predicted normal FEV_1), there was a tendency toward better lung function in female patients that did not reach statistical significance (Table 1). The mean dose of α_1-Pi given IV was 62.2 ± 9.3 mg/kg of body weight.

The majority of patients had moderately to severely impaired lung function. Sixty patients had an FEV_1 on their first visit between 30% and 65% of predicted (group 2); in 25 patients, it was < 30% of

Table 1—*Demographic Data for 96 Patients With Severe α_1-Pi Deficiency**

Variables	Total	Female Patients	Male Patients	p Value
Patients, No.	96	34	62	0.004
Age at first FEV_1, yr	44.3 ± 8.6	46.0 ± 9.2	43.4 ± 8.2	NS
Phenotypes, No.				
PiZ	85	27	58	
PiSZ	8	5	3	NS
Other	3	2	1	
Smoking status, No.				
Never-smoker	12	6	6	
Smoker	14	4	24	NS
Ex-smoker	70	24	46	
Pack-years (only smokers/ex-smokers), No.	20.2 ± 13.2	15.6 ± 10.6	22.6 ± 13.9	0.0272
BMI, kg/m^2	22.9 ± 3.6	22.5 ± 4.3	23.0 ± 3.2	NS
Follow-up before augmentation therapy, mo	47.5 ± 28.1	42.1 ± 22.4	50.4 ± 30.5	NS
Follow-up during augmentation therapy, mo	50.2 ± 30.2	53.4 ± 27.2	48.4 ± 31.8	NS
FEV_1 measurements before augmentation therapy, No.	4.9 ± 2.6	5.0 ± 3.1	4.8 ± 3.2	NS
FEV_1 measurements during augmentation therapy, No.	7.7 ± 4.3	7.8 ± 3.7	7.7 ± 4.6	NS
First available FEV_1, L/s	1.43 ± 0.65	1.24 ± 0.56	1.53 ± 0.68	0.028
First available FEV_1, % of predicted normal	41.0 ± 17.3	45.2 ± 19.5	38.8 ± 15.7	0.083

*Data are presented as mean ± SD unless otherwise indicated. NS = not significant; BMI = body mass index.

predicted (group 1); and in 11 patients, it was > 65% of predicted (group 3). Neither sex, smoking habits, nor phenotype were predictors of severity of the disease. There was a tendency toward a smaller number of pack-years in group 3, but because of large standard deviations, this did not reach statistical significance (Table 2). There was also no difference in the follow-up time or number of FEV_1 measurements before augmentation therapy was started, but both follow-up time and number of available FEV_1 measurements during augmentation therapy were significantly higher for patients with better lung function (Table 2).

The mean number of cigarettes smoked was similar for smokers and ex-smokers, but women had smoked significantly less than men (15.6 ± 10.6 pack-years vs 22.6 ± 13.9 pack years, $p = 0.0271$). There was a statistically significant dependency between smoking habits and age: smokers were approximately 10 years younger than ex-smokers and nonsmokers ($p = 0.0013$); however, no difference was found for FEV_1 percent predicted, indicating that smokers, ex-smokers, and nonsmokers were identified and/or recruited for the registry at roughly the same degree of lung function impairment.

Analysis of FEV_1 Courses Over Time

By grouping the patients according to the severity of their lung function impairment on their first presentation, there was a significant lower decline in FEV_1 during the time the patients received augmentation therapy compared to the period without treatment (Table 3). For patients who had severe lung function impairment on entrance to the study, there was no difference between pretreatment and treatment ΔFEV_1. Patients with moderate lung function impairment had a small reduction in ΔFEV_1 that did not quite reach the level of statistical significance. The 11 patients with FEV_1 > 65% had a large and a statistically significant reduction in the decline in FEV_1.

When the patients were grouped according to their lung function at the beginning of augmentation therapy, patients with FEV_1 < 30% showed a statistically significant slowdown of the decline from 53.4 ± 45.3 mL/yr to 22.1 ± 16.0 mL/yr during the treatment period ($p < 0.0001$). The changes for patients with either mild or moderate lung function impairment were not significant for this time point.

Because the mean ΔFEV_1 for patients in group 3 changed considerably depending on whether grouped by their first available FEV_1 or the FEV_1 at the beginning of therapy, the group of patients with FEV_1 > 65% was reanalyzed after identifying rapid decliners and slow decliners (Fig 1). Rapid decliners were defined as having had a FEV_1 > 65% on the first visit and < 65% at the beginning of therapy. Their mean FEV_1 was 79.6 ± 13.5% at the first presentation with a mean ΔFEV_1 of 255.7 ± 70.4 mL/yr. The FEV_1 had declined to 45.8 ± 12.0% when augmentation therapy was started. Afterwards, the ΔFEV_1 was reduced to 52.7 ± 61.3 mL/yr during therapy ($p = 0.0016$). Slow decliners were patients with FEV_1 > 65% during their whole observational period without augmentation therapy. Their mean FEV_1 was 80.6 ± 6.8% when included in the registry and 80.6 ± 11.2% when IV α_1-Pi treatment was started.

There was no difference in the smoking status between the groups; there were four ex-smokers and two smokers among the rapid decliners, and two ex-smokers, one smoker, and one never-smoker among the slow decliners.

Interindividual Comparison of FEV_1

So far, the analysis of the FEV_1 compared data before and during augmentation therapy using each

Table 2—*Data on Follow-up in Relation to Lung Function Impairment**

Variables	FEV_1 < 30% of Predicted	FEV_1 30 to 65% of Predicted	FEV_1 > 65% of Predicted	p Value
Male/female gender, No.	17/8	39/21	6/5	NS
Smoking status, No.				
Smoker	2	9	3	NS
Ex-smoker	21	42	7	
Never-smoker	12	9	1	
Age, yr	45.5 ± 7.5	44.6 ± 8.8	40.1 ± 9.8	NS
Pack-years, No.	21.7 ± 12.1	20.6 ± 14.2	15.2 ± 10.8	NS
Follow-up before augmentation therapy, mo	50.7 ± 34.3	44.3 ± 9.4	50.4 ± 8.9	NS
Follow-up with augmentation therapy, mo	36.7 ± 23.3	51.9 ± 31.2	70.4 ± 27.1	0.0021
FEV_1 measurements before augmentation therapy, No.	5.1 ± 2.3	4.8 ± 2.5	4.9 ± 3.2	NS
FEV_1 measurements with augmentation therapy, No.	5.5 ± 2.9	8.4 ± 4.6	9.3 ± 3.4	0.0041

*Data are presented as mean ± SD unless otherwise indicated. See Table 1 for abbreviation.

Table 3—*Decline in FEV_1 for Nontreatment and Treatment Periods**

Variables	ΔFEV_1 Before Therapy With α_1-Pi, mL/yr	ΔFEV_1 During Therapy With α_1-Pi, mL/yr	Difference Between Treatment and Nontreatment	p Value
Total (n = 96)	− 49.2 ± 60.8	− 34.3 ± 29.7	14.9 ± 61.4	0.019
First available FEV_1				
< 30% (n = 25)	− 15.3 ± 38.5	− 19.0 ± 18.0	− 3.7 ± 48.6	NS
30 to 65% (n = 60)	− 49.3 ± 43.4	− 37.8 ± 25.0	11.6 ± 48.8	0.066
> 65% (n = 11)	− 122.5 ± 108.4	− 48.9 ± 54.9	73.6 ± 107.0	0.045
Rapid decliners (n = 7)	− 255.7 ± 70.4	− 52.7 ± 61.3	203.0 ± 99.2	0.001
Slow decliners (n = 4)	15.9 ± 128.8	− 10.6 ± 66.0	− 26.4 ± 89.5	NS

*Data are presented as mean ± SD. See Table 1 for abbreviation.

patient's data as his own control (intraindividual comparison). Another approach to analysis is to group patients with the same degree of lung function impairment before and during therapy with α_1-Pi and compare the ΔFEV_1 between the groups (interindividual comparison). Figure 2 shows the decline of ΔFEV_1 patients with $FEV_1 > 65\%$ predicted with and without augmentation therapy. The ΔFEV_1 for patients receiving IV α_1-Pi was significantly less than for untreated patients.

Discussion

This study is the first intraindividual study comparing lung function decline in 96 patients with α_1-Pi deficiency before they received augmentation therapy to a period of time in which they received weekly IV augmentation therapy. There was a significantly lower decline in FEV_1 during the period patients received IV augmentation therapy compared to the period without specific treatment. The overall reduction of the decline in FEV_1 from 49.2 to 34.3 mL/yr by 15 mL/yr is similar to the reduction previously reported by studies comparing a group of treated with a group of untreated individuals with α_1-Pi deficiency.[6,7] The ΔFEV_1 during the period in that the patients received augmentation therapy is comparable with that of normal nonsmoking individuals.[12,13]

Of special interest is the subgroup of patients with an initial FEV_1 of > 65% predicted. If their lung

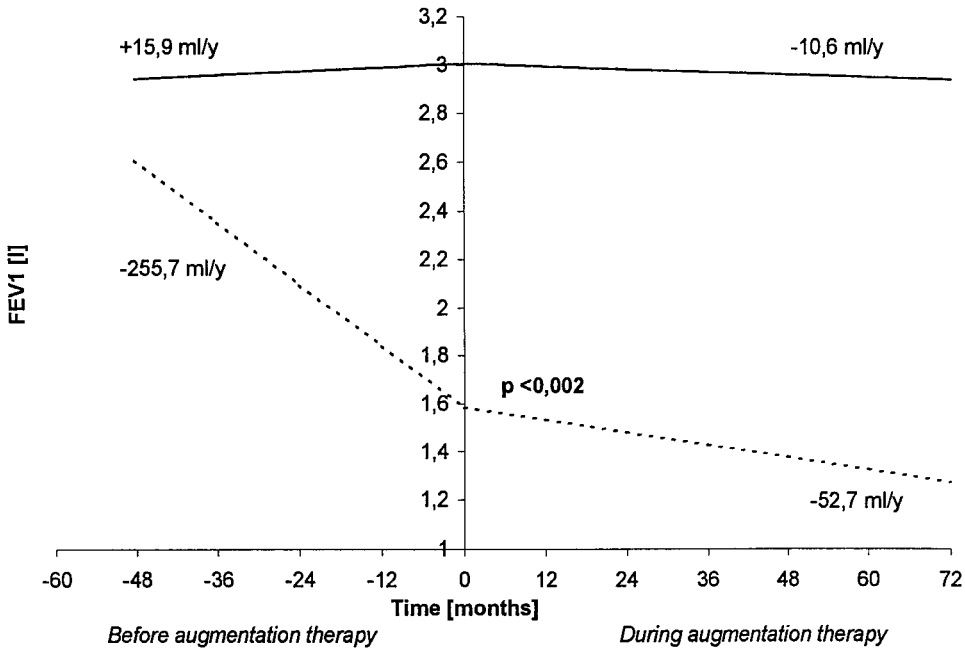

FIGURE 1. Change of FEV_1 in patients with $FEV_1 > 65\%$. Rapid decliners (n = 7, dotted lines) are patients with $FEV_1 > 65\%$ at the time of diagnosis that declined to FEV_1 values < 65% during the time they did not receive augmentation therapy. The ΔFEV_1 was significantly reduced during the treatment period ($p < 0.0016$). Slow decliners (n = 4, solid lines) had stable values for FEV_1 before treatment with α_1-Pi.

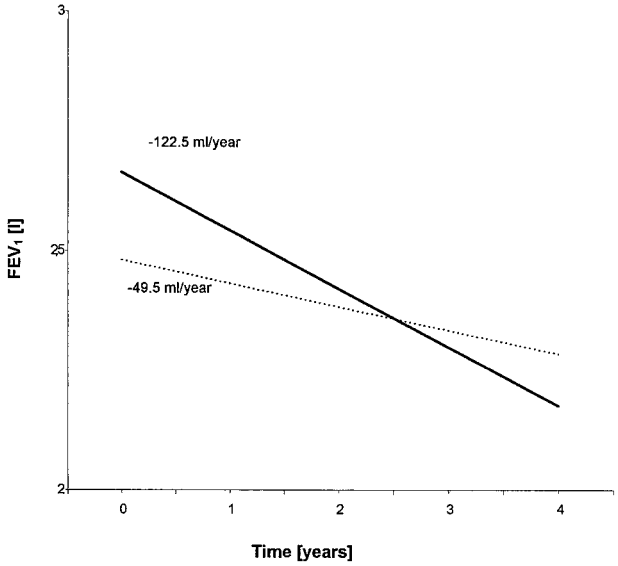

FIGURE 2. Interindividual comparison of the decline of patients with $FEV_1 > 65\%$ not receiving augmentation therapy (solid line) and those with $FEV_1 > 65\%$ during augmentation therapy (dotted line).

function could be stabilized at that level, they could continue to live an active lifestyle and thus limit the negative impact of their disease on medical, social, and financial aspects. In patients with a first $FEV_1 > 65\%$ of predicted, there was a significant reduction of ΔFEV_1 by 74 mL/yr (from initially 123 mL/yr without treatment to 49 mL/yr with treatment). If the analysis was limited to patients that declined to FEV_1 values $< 65\%$ of predicted until augmentation therapy was started (rapid decliners), the reduction in ΔFEV_1 was as high as 203 mL/yr.

Despite the potential drawback of not having a randomized control group in this data set, this study has indeed the clear advantage of intraindividually comparing longitudinal data before and during augmentation therapy. But, according to the natural history of the disease and the mode of action of the augmentation therapy, there is no theoretical chance of improving the lung function in any state of the disease. In consequence and according to the (more or less) arbitrary onset of observation of each patient before therapy and the (more or less) arbitrary onset of therapy in each individual patients' history, a fair comparison needs to account for the different degrees of impairment at onset of therapy as compared to that at the onset of observation for each patient under inspection as well. This is also because of the already proven dependency between degree of lung function impairment and effect of augmentation therapy.[6,7] This led us to undertake also a "classical" interindividual comparison for patient subgroups with comparable lung function impairment at start of observation and at start of therapy. To increase the comparability of those interindividual comparisons with previously reported data, we did an interindividual comparison of patients with $FEV_1 > 65\%$ of predicted both without (start of observation to the beginning of augmentation therapy) and with augmentation therapy (onset of therapy until last available FEV_1). This analysis also showed a slower decline for treated patients.

The results of both intraindividual and interindividual comparison contrast those of the US registry, which showed little or no decline in FEV_1 in patients with well-preserved lung function.[7] However, despite well-preserved lung function in both, the groups differ in respect to their lung disease. While the US registry patients with well-preserved lung function were mainly recruited as nonindex cases from family studies and patients with liver disease,[14] our patients were recruited as index cases and a decline of > 120 mL/yr was required to qualify for augmentation therapy when FEV_1 was $> 65\%$ of predicted. Consequently and in accordance with previous studies,[15,16] US patients showed little or no decline in lung function, whereas most of our patients presented with a very rapid decline in FEV_1. It was in these patients that augmentation therapy had the most dramatic effect and the ΔFEV_1 could be reduced by 203 mL/yr. The four patients with normal lung function and without a decline in FEV_1 before augmentation therapy did not have any significant change in lung function during the treatment period. In retrospect, these patients did not fulfill inclusion criteria for augmentation therapy.

In patients with moderately impaired lung function, the difference in ΔFEV_1 between treatment and nontreatment periods was small and did not reach statistical significance. This is in contrast to the results of the US registry and Danish-German study, which both showed a reduction of ΔFEV_1 in this group of patients.[6,7] This is because of several factors. First of all, this group was too small to demonstrate a significant difference because of augmentation therapy, given the low ΔFEV_1. Also, in comparison to the US registry and the Danish-German study, the loss of FEV_1 in patients with moderately impaired lung function was substantially lower in this study. A longer time of follow-up poses a selection bias toward lower ΔFEV_1 because patients with a high ΔFEV_1 are more likely to drop out because of lung volume reduction surgery, lung transplant, or death. Also, because of a kind of a "survivor effect," a longer follow-up time in itself will

result in a lower ΔFEV_1. At the same time, this will render the detection of a significant difference between treatment and nontreatment periods more difficult. The calculated *post hoc* power of the test on ΔFEV_1 within the group of patients with initial FEV_1 between 30% and 65% of predicted was only 44%. To illustrate this further, a prospective study to prove an identical treatment effect as seen in our investigation (ΔFEV_1 11.6 mL/yr) would need to include 141 patients with a similar mean follow-up time as in this study (approximately 96 months). This explains the nonsignificant test result between treatment and nontreatment periods in patients with FEV_1 between 30% and 65% of predicted. Compared to recently published[17] sample-size estimations based on the variance of FEV_1 measurements of the US registry, the theoretically required sample size seems moderate.

Not surprisingly, the loss of FEV_1 of 25 patients with a first $FEV_1 < 30\%$ of predicted was low and did not further decline during the treatment period. If the group is broadened to include all patients with a FEV_1 of $< 30\%$ at the beginning of augmentation therapy ($n = 38$), a statistically significant difference was found between treatment and nontreatment periods ($p < 0.0001$). This may be because some rapid decliners, *ie*, patients who declined from moderate to severe emphysema during the period they did not receive augmentation therapy, skewed the results toward a higher ΔFEV_1 before treatment (53.4 mL/yr vs 15.3 mL/yr for the remaining patients [slow decliners]). Because the ΔFEV_1 during the treatment period is very similar (19.0 mL/yr vs 22.1 mL/yr), these patients may have profited most from augmentation therapy. It is known, however, that the ΔFEV_1 decreases with increasing lung function impairment,[5–7] so that this finding may also be in part attributed to the natural course of the disease.

In this study, there were twice as many male as female patients. Similar findings have been reported previously[18–20] and have ascribed this to the difference in smoking habits between the genders.[20] In nonsmokers in this study and other studies,[5,20] the percentage of male and female subjects was equal. The US registry and the Danish registry report similar numbers of male and female subjects in their registries. This may be partially because of the higher number of nonindex case patients included who are predominantly female subjects[7,16,21]; however, other factors may also have an influence on the gender distribution.

No difference was found for FEV_1 in percent predicted between smokers, ex-smokers, and nonsmokers. There was a tendency toward better lung function in female subjects, but this did not reach the level of statistical significance. Also, for the groups with different degree of lung function impairment, there were no differences in age, smoking history, and gender. This indicates that patients were identified and/or recruited by the registry with all degrees of lung function impairment regardless of smoking history and gender. Time of observation and number of available FEV_1 measurements were significantly lower in patients with poor lung function, which is attributable to a higher rate of lung surgery or death (data not shown) in this subgroup, limiting the number of valid data for analysis.

As shown by other studies,[15,22,23] never-smokers were approximately 10 years older than smokers with similar lung function impairment, which is attributed to the lower load of oxidants and proteases in never-smokers. However, the reason for the missing age difference between ex-smokers and never-smokers is not clear. It can be speculated that the never-smokers included in this study differ in respect to age of onset of lung function impairment and progression of the disease that made them more likely to be included. In contrast, the majority of never-smoking α_1-Pi–deficient individuals have a lower risk of developing emphysema,[16] they may therefore escape detection, and they have a smaller probability of being included.[15] This may explain the apparent selection bias.

In conclusion, this study shows a significant reduction in the loss of lung function during the period in which patients with α_1-Pi deficiency received augmentation therapy, reflecting a slower progress of their lung emphysema. Patients with a rapid decline in FEV_1 before augmentation therapy was started had the highest reduction in ΔFEV_1. Although this is not a double-blind, placebo-controlled trial (but rather a retrospective set of partially controlled n-of-1 trials as discussed previously), the data are in keeping with results of previously published studies indicating that certain subsets of patients may profit from augmentation therapy.[5–7] In the absence of controlled trials showing the efficacy of IV therapy with human α_1-Pi, and considering that results of such trials will not be available for at least another 5 years, the results of this study are yet another piece of evidence indicating that augmentation therapy can slow the progression of pulmonary emphysema. In this study, patients with well-maintained lung function and a rapid decline profited most from augmentation therapy. Early diagnosis and close follow-up are needed to identify patients at risk and to start augmentation therapy with IV α_1-Pi, even if lung function is $> 65\%$ predicted.

Appendix

Additional Participants of the WATL Group for α_1-Pi Deficiency

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