

## Does $\alpha_1$ -antitrypsin augmentation therapy slow the annual decline in FEV<sub>1</sub> in patients with severe hereditary $\alpha_1$ -antitrypsin deficiency?

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*Does  $\alpha_1$ -antitrypsin augmentation therapy slow the annual decline in FEV<sub>1</sub> in patients with severe hereditary  $\alpha_1$ -antitrypsin deficiency? N. Seersholm, M. Wencker, N. Banik, K. Viskum, A. Dirksen, A. Kok-Jensen, N. Konietzko for the "Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL)  $\alpha_1$ -AT study group". ©ERS Journals Ltd 1997.*

**ABSTRACT:** Patients with severe hereditary  $\alpha_1$ -antitrypsin deficiency ( $\alpha_1$ -ATD) face a high risk of developing emphysema at a young age. Intravenous augmentation therapy with purified human  $\alpha_1$ -antitrypsin ( $\alpha_1$ -AT) is now available. However, a controlled trial to show its efficacy has never been carried out. The aim of this study was to compare the decline in forced expiratory volume in one second ( $\Delta$ FEV<sub>1</sub>) between Danish patients who had never received augmentation therapy and German patients treated with weekly infusion of  $\alpha_1$ -AT.

From the files of the Danish  $\alpha_1$ -ATD register, 97 exsmokers, with a PiZ phenotype and for whom results of at least two lung function measurements with an interval of at least 1 yr were available, were identified. From a German group of patients treated with weekly infusions of  $\alpha_1$ -AT, 60 mg·kg<sup>-1</sup> body weight, 198 exsmokers, with biannual lung function measurements were identified. The  $\Delta$ FEV<sub>1</sub> was compared between the two treatment groups by random effects modelling.

The  $\Delta$ FEV<sub>1</sub> in the treated group was significantly lower than in the untreated group, with annual declines of 53 mL·yr<sup>-1</sup> (95% confidence interval (95% CI) 48–58 mL·yr<sup>-1</sup>) and 75 mL·yr<sup>-1</sup> (95% CI 63–87 mL·yr<sup>-1</sup>), respectively (p=0.02). The two groups differed with respect to gender and initial FEV<sub>1</sub>% predicted. Gender did not have any influence on the  $\Delta$ FEV<sub>1</sub>. Stratification by initial FEV<sub>1</sub>% pred showed a significant effect of the treatment only in the group of patients with an initial FEV<sub>1</sub>% pred of 31–65%, and  $\Delta$ FEV<sub>1</sub> was reduced by 21 mL·yr<sup>-1</sup>.

This nonrandomized study suggests that weekly infusion of human  $\alpha_1$ -antitrypsin in patients with moderately reduced lung function may slow the annual decline in forced expiratory volume in one second.

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Alpha<sub>1</sub>-antitrypsin deficiency ( $\alpha_1$ -ATD) is a disorder inherited in an autosomal recessive pattern, with codominant alleles known as the protease inhibitor system (Pi). The main function of  $\alpha_1$ -antitrypsin ( $\alpha_1$ -AT) is to protect the lungs against a powerful elastase released from neutrophil leucocytes [1, 2]. In severe  $\alpha_1$ -ATD, genotype PiZZ, this protection is compromised leading to accelerated decline in forced expiratory volume in one second ( $\Delta$ FEV<sub>1</sub>). As a result, the patients may develop emphysema at a young age, with cigarette smoking being the most significant additional risk factor [3, 4].

The only treatments currently available are smoking cessation, symptomatic treatment similar to the treatment of chronic obstructive pulmonary disease (COPD), and, as a last resort, lung transplantation [5].

It has been shown that weekly or monthly infusion of human  $\alpha_1$ -AT is effective in raising serum  $\alpha_1$ -AT levels with few adverse effects and, theoretically, this should inhibit the development of emphysema [6–9]. However,

a randomized, placebo-controlled study evaluating whether augmentation therapy is capable of slowing down further development of emphysema, has not yet been carried out. In a rare disease, such a study would be hampered by the difficulty of recruiting a sufficient number of patients. The follow-up time should be 3–5 yrs due to a high intra-individual variability of lung function measurements and the relatively slow progression of emphysema [10]. Several uncontrolled trials have been initiated, but the results are not yet available [11].

Despite the lack of proof of efficacy, the American Food and Drug Administration (FDA) approved treatment of  $\alpha_1$ -ATD with purified human  $\alpha_1$ -AT in December 1987 as an orphan drug. The purpose of this nonrandomized study was to evaluate the efficacy of augmentation therapy in patients with  $\alpha_1$ -ATD by directly comparing the  $\Delta$ FEV<sub>1</sub> in a German group of patients treated with  $\alpha_1$ -AT with the  $\Delta$ FEV<sub>1</sub> in an untreated group of Danish patients.

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## Methods

### The German group

A referral population of patients with severe  $\alpha_1$ -ATD was included in a drug surveillance study of augmentation therapy, if they fulfilled the following criteria: 1) Pi serum levels less than 35% of normal, regardless of phenotype; 2) impaired lung function, with either FEV<sub>1</sub> of less than 65% pred or an annual decline in FEV<sub>1</sub> of more than 120 mL; and 3) nonsmoking at the time of enrolment. All patients received weekly augmentation therapy with 60 mg·kg<sup>-1</sup> body weight human  $\alpha_1$ -AT (ProLactin® HS; Bayer, Leverkusen, Germany). A total of 25 centres participated in the German study under the auspices of the Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL). The project was approved by the Ethics Committee.

Lung function measurements were carried out at the study centres before commencing augmentation therapy, 1 week after the beginning of the study, after 3 and 6 months, and then every 6 months. The measurements were performed in accordance with European recommendations by specially trained personnel [12]. Post-bronchodilator FEV<sub>1</sub> was measured after two puffs of salbutamol, 0.1 mg·puff<sup>-1</sup>, and the best out of a minimum of three trials was recorded.

Patients were asked about their smoking habits before enrolment and classified as lifetime nonsmokers, exsmokers or current smokers. Smoking status was defined as follows: a smoker was a person who had smoked at least 20 packs of cigarettes or at least one cigarette·day<sup>-1</sup> for at least 1 yr in a lifetime [13]; an ex-smoker was a person who had abstained from smoking for at least 3 months and had not resumed smoking. Current smokers qualified for augmentation therapy only if they agreed to stop smoking.

To make the treated German group as comparable as possible with the untreated Danish group, the German patients included in the present analysis should meet the following inclusion criteria: have the PiZZ phenotype; be exsmokers before entering the surveillance study; have received augmentation therapy for at least 1 yr; and have had two or more spirometries at least 1 yr apart performed during the treatment period. Of the 443 patients included in the surveillance study: 42 were not PiZZ; 99 were current smokers or lifetime nonsmokers; and 104 had either missing postbronchodilator values or had received augmentation therapy for less than 1 yr.

### The Danish group

Patients were selected from The Danish  $\alpha_1$ -Antitrypsin Deficiency Register in Copenhagen, which was initiated in 1978. Alpha<sub>1</sub>-ATD patients are referred by physicians throughout Denmark ("index cases"), and once a patient is registered a family record is obtained and members at risk of having a Z-gene are offered an examination of their Pi-type, in order to identify subjects not necessarily suffering from pulmonary symptoms ("non-index cases").

The  $\alpha_1$ -antitrypsin Pi-type was determined by the Department of Clinical Chemistry at Bispebjerg Hospital

by isoelectric focusing, as described by FAGERHOL and COX [14]. If phenotyping had not been performed, the patients were assumed to have phenotype PiZZ or PiZO if their  $\alpha_1$ -AT serum level was less than 12  $\mu$ mol·L<sup>-1</sup>.

Lung function measurements (spirometry) of the patients in the register were either reported by the referring physician or performed at the chest clinic in Copenhagen. Measurements were performed in accordance with European recommendations [12]. Smoking status was defined in the same way as for the German group.

Patients eligible for the present study were identified as Pi-type ZZ or having a  $\alpha_1$ -AT serum level of less than 12  $\mu$ mol·L<sup>-1</sup>. The patients should: be exsmokers; be index cases; be more than 25 yrs of age at entry; and have results of two or more spirometries at least 1 yr apart available.

### Statistical analysis

For both groups, predicted values of FEV<sub>1</sub> were calculated according to European reference equations [12].

The decline in FEV<sub>1</sub> was analysed by random effects modelling [15, 16], which included age at entry and follow-up time as covariates, treatment (Denmark *versus* Germany), gender, and initial FEV<sub>1</sub> as fixed parameters, and the individual patients as random effects parameters. The model fit was performed using the PROC MIXED module of the Statistical Analysis System (SAS) software (SAS-Institute, Cary, NC, USA, 1992). A p-value of less than 0.05 was taken to be statistically significant.

## Results

A total of 295 patients were available for analysis, with 97 in the untreated Danish group and 198 in the treated German group. Initial FEV<sub>1</sub> % pred was significantly lower in the treated group compared with the untreated group (37 *versus* 42%; p=0.02), and there were significantly more males in the treated group (72 *versus* 57%; p<0.01) (table 1). The average follow-up time was 3.2 yrs in the treated group and 5.8 yrs in the untreated group (p<0.01). The age at entry into the study was not significantly different between the two groups (table 1).

Overall there was a significant difference of 22 mL·yr<sup>-1</sup> in  $\Delta$ FEV<sub>1</sub> between the two groups, with 53 mL·yr<sup>-1</sup> (95% confidence interval (95% CI) 48–58 mL·yr<sup>-1</sup>) in the treated German group as compared with 75 mL·yr<sup>-1</sup>

Table 1. – Demographic data for the treated German group and the untreated Danish group

	Groups		p-value
	Treated (German)	Untreated (Danish)	
Patients n	198	97	
Sex M/F	142/56	55/42	0.01
Initial FEV <sub>1</sub> % pred	37 (14)	42 (10)	0.02
Age at entry yrs	46 (8)	45 (10)	NS
Follow-up yrs	3.2 (1.6)	5.8 (3.4)	<0.01

Data are presented as absolute value, or mean and SD in parenthesis. M: male; F: female; FEV<sub>1</sub>: forced expiratory volume in one second; % pred: percentage of predicted value; NS: non-significant.

Table 2. – Annual  $\Delta$ FEV<sub>1</sub> for the treated German group and the untreated Danish group stratified by initial FEV<sub>1</sub> % predicted

	Groups				p-value
	Treated (German)		Untreated (Danish)		
	Pts n	$\Delta$ FEV <sub>1</sub> mL·yr <sup>-1</sup>	Pts n	$\Delta$ FEV <sub>1</sub> mL·yr <sup>-1</sup>	
<b>Initial FEV<sub>1</sub></b>					
≤30% pred	75	24.2 (23.6)	27	30.9 (36.3)	0.6
31–65% pred	112	61.8 (25.3)	58	82.8 (49.3)	0.04
>65% pred	11	162.0 (28.7)	12	140.0 (83.2)	0.7
<b>Total</b>	<b>198</b>	<b>53.0 (37.6)</b>	<b>97</b>	<b>74.5 (59.6)</b>	<b>0.02</b>

Data are presented as absolute number (of patients), and as mean and SD in parenthesis.  $\Delta$ FEV<sub>1</sub>: decline in forced expiratory volume in one second.

(95% CI 63–87 mL·yr<sup>-1</sup>) in the untreated Danish group ( $p=0.02$ ).

To explore whether this difference in  $\Delta$ FEV<sub>1</sub> was due to differences in gender, follow-up time, and initial FEV<sub>1</sub> % pred between the two groups, the impact of these variables was analysed. Neither gender alone nor the interaction terms of gender and treatment had a significant influence on  $\Delta$ FEV<sub>1</sub> ( $p=0.64$ ). Follow-up time was analysed as a continuous variable and had no significant influence on  $\Delta$ FEV<sub>1</sub> ( $p=0.46$ ). The initial FEV<sub>1</sub> % pred was divided in three strata: ≤30, 31–65 and >65%, which were included in the model. The  $\Delta$ FEV<sub>1</sub> increased significantly with increasing FEV<sub>1</sub> % pred both in the treated and untreated groups (table 2). There was no significant difference in  $\Delta$ FEV<sub>1</sub> between the treated group and the untreated group among the patients with the lowest and the highest FEV<sub>1</sub> % pred. Among the patients with an initial FEV<sub>1</sub> of 31–65% pred,  $\Delta$ FEV<sub>1</sub> was significantly lower among the treated patients ( $p=0.04$ ); their  $\Delta$ FEV<sub>1</sub> was 62 mL·yr<sup>-1</sup> (95% CI 57–67 mL·yr<sup>-1</sup>) as compared with 83 mL·yr<sup>-1</sup> (95% CI 70–96 mL·yr<sup>-1</sup>) in the untreated group. Subdivision of this group did not change the results any further.

### Discussion

This study is the first attempt to evaluate the effect of  $\alpha_1$ -antitrypsin augmentation therapy on patients with  $\alpha_1$ -ATD deficiency by comparing the annual decline in FEV<sub>1</sub> in a treated (nonrandomized) group of exsmokers in Germany and an untreated group of exsmokers in Denmark. We found a significantly slower  $\Delta$ FEV<sub>1</sub> in the treated group compared with the untreated group. Furthermore, stratification by initial FEV<sub>1</sub> % pred showed that the effect was present only in the group of patients with an initial FEV<sub>1</sub> of 31–65% pred, where the benefit was a reduction in  $\Delta$ FEV<sub>1</sub> of 21 mL·yr<sup>-1</sup>. This is particularly relevant, because the majority of the patients have FEV<sub>1</sub> values in this range when the condition is confirmed.

This is not a randomized study and there are several possible interpretations of the results. The main question is whether the lower  $\Delta$ FEV<sub>1</sub> in the German patients was due to treatment or to confounding factors, such as smoking history, gender, age, length of follow-up, and lung function. Great care was taken to make the two groups comparable, and by including only exsmokers we have avoided the problem of current smokers having a higher  $\Delta$ FEV<sub>1</sub> than exsmokers, as was the case in a previous study of the Danish patients [5]. Furthermore,

only index cases were included because all the German patients were index cases.

The age at entry was not different between the groups, but they differed significantly with respect to gender, follow-up time, and initial FEV<sub>1</sub>. There was no difference in  $\Delta$ FEV<sub>1</sub> between males or females overall or within treatment groups, and this factor cannot explain the results. The variable follow-up time was analysed both as a continuous variable and as a categorical variable, and there were no effects on  $\Delta$ FEV<sub>1</sub> in either analysis.

The initial FEV<sub>1</sub> is the most troublesome parameter because  $\Delta$ FEV<sub>1</sub> varies with varying FEV<sub>1</sub>. In a previous Danish study, including index and nonindex cases, the highest  $\Delta$ FEV<sub>1</sub> was found in patients with moderately reduced lung function, and patients with lower or higher initial FEV<sub>1</sub> had slower decline (U-shaped relationship) [5]. In the present study,  $\Delta$ FEV<sub>1</sub> decreased with decreasing initial FEV<sub>1</sub> in both groups. The apparent low  $\Delta$ FEV<sub>1</sub> among patients with low initial FEV<sub>1</sub> is most likely to be due to a survivor effect; patients with fast decline in lung function die before they can generate enough data points for calculation of  $\Delta$ FEV<sub>1</sub>. The high  $\Delta$ FEV<sub>1</sub> in patients with an initial FEV<sub>1</sub> above 65% pred in both groups is probably due to selection bias. One of the selection criteria for including patients in the German study was that they should have a FEV<sub>1</sub> <65% pred or that they should have a  $\Delta$ FEV<sub>1</sub> of >120 mL·yr<sup>-1</sup>. In the Danish group, the index cases were selected for this study because they had at least two spirometries at least 1 yr apart. Thus, patients in both groups with FEV<sub>1</sub> >65% pred are subject to selection bias, with fast decline in lung function.

The reason for the difference in  $\Delta$ FEV<sub>1</sub> being statistically significant only in the group with initial FEV<sub>1</sub> of 31–65% pred was due, in part, to small numbers in the two extreme groups and, in part, to a stronger selection bias in the German group, with FEV<sub>1</sub> >65% pred; *i.e.* they should have a  $\Delta$ FEV<sub>1</sub> of more than 120 mL·yr<sup>-1</sup> to be included.

This nonrandomized study indicates a beneficial effect of augmentation therapy in patients with an initial forced expiratory volume in one second of 31–65% pred. However, a randomized, placebo-controlled trial should render definitive evidence for a clinical effect.

### Appendix

Participants of the German WATL group on  $\alpha_1$ -antitrypsin deficiency were: R. Loddenkemper, N. Schönfeld (Berlin); E. Kaukel, R-D. Staud (Hamburg); G. Kanzow (Großhansdorf); K. Wießmann (Lübeck); U. Lepp (Borstel); N. de Wall (Sande); K. Eberhardt (Bremen); H. Fabel (Hannover); G. Goeckenjan (Immenhausen); R. Kappes (Duesseldorf); E.W. Schmidt (Bochum); H. Steveling (Essen); J. Lorenz, J. Schlegel, W. Schmidt (Mainz); R. Buhl (Frankfurt); V. Schulz (Heidelberg); R. Dierkesmann (Gerlingen); C. Virchow (Freiburg); M. Schwaiblmaier, W. Hauk (Munich); N. Weber (Gauting); D. Nolte, W. Petro (Bad Reichenhall); B. Wiesner, D. Treutler (Bad Berka).

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