Early View

Original article

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Long-term effect of alpha-1-antitrypsin augmentation therapy on the decline of FEV$_1$ in deficient patients: An analysis of the AIR database

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Take home message: Our analysis of European real-world follow-up data of FEV1 %predicted in ZZ-AATD patients showed no difference in annual FEV1 decline between the iv AAT augmentation treated and untreated patients over a period of more than 8 years.
Abstract

**Background** Patients with ZZ (Glu342Lys) alpha-1-antitrypsin deficiency (ZZ-AATD) who received augmentation therapy with alpha-1-antitrypsin (AAT) in randomized controlled trials over 2 - 3 years, failed to show a significant reduction of the annual decline of FEV₁.

**Methods** To compare the trajectory of FEV₁ change during 4 or more years in ZZ-AATD patients with emphysema receiving or not receiving intravenous augmentation therapy, a retrospective analysis of FEV₁ values entered in the Alpha-1 International Registry (AIR) of ZZ-AATD patients from five different European countries: Germany, UK, Spain, Italy and The Netherlands was performed. The post-bronchodilator FEV₁,%predicted values for baseline and follow-up over time from patients were analysed using linear mixed effects models.

**Results** Data of 374 patients were analysed: 246 untreated and 128 treated with intravenous AAT augmentation therapy. The mean follow-up duration of the untreated group was 8.60 (SD ± 3.34) years and 8.59 (± 2.62) years for the treated group. The mixed effects model analysis showed a mean FEV₁ decline of -0.931% predicted per year (95% confidence interval -1.144 to -0.718) in the untreated group and a decline of -1.016 % predicted per year (-1.319 to -0.7145) in the treated group. The likelihood ratio test showed no difference between the two groups (p = 0.71).

**Conclusion** In our study population, we could not detect a significant difference in the annual decline of FEV₁ by AAT augmentation treatment over an average period of 8.6 years. Other approaches are needed to validate any benefit of augmentation therapy.
Introduction

Severe alpha-1-antitrypsin deficiency (AATD) is a hereditary disorder that can predispose to emphysema dominant lung disease, and to an accelerated decline in forced expiratory volume in one second (FEV$_1$) at an early age, due to low serum alpha-1-antitrypsin (AAT) levels. The ZZ-AATD (Glu342Lys) phenotype is the most common deficiency with highly variable lung impact, ranging from no symptoms to the development of AATD-related emphysema (1, 2). ZZ-AATD patients with an accelerated annual decline in FEV$_1$ have a poorer prognosis, as a lower FEV$_1$ is a predictor for all-cause and respiratory mortality (3-5).

More than twenty-five years ago, AAT augmentation therapy was introduced in the United States and some European countries. Based on the demonstration of a rise in serum AAT level above a putative ‘protective threshold’ and the elevation of the level of AAT in bronchoalveolar lavage fluid, with weekly infusions, it was assumed that substitution of the reduced serum levels in ZZ-AATD patients with AAT purified from blood of healthy donors, would protect from further progression of lung disease (6). The ATS/ERS statement recommends weekly AAT augmentation therapy with 60mg/kg body weight, for AATD patients with alpha-1-antitrypsin serum levels below the putative protective threshold of 11.0uM and an FEV$_1$ between 30 and 65% predicted based on follow up data of the National Heart, Lung, and Blood Institute (NHLBI) registry (5) (7). A subsequent meta-analysis suggested efficacy (8) although a systematic review (9) did not confirm a beneficial effect on annual decline in FEV$_1$ in ZZ-AATD patients who received AAT augmentation treatment compared to those who did not.

The rate of the annual FEV$_1$ decline is independently associated with the severity of emphysema, as quantified by lung densitometry (10). Indeed lung densitometry can quantify pulmonary emphysema accurately, and is a more sensitive and specific method to assess emphysema progression than the FEV$_1$ (11). Based on this validation, lung densitometry has been used as the outcome parameter in several placebo-controlled randomized clinical trials to determine the effect of intravenous (iv) AAT stable.
augmentation treatment on preservation of lung tissue. A consistent protective effect of iv AAT on lung tissue has been reported in relatively short-term studies of 2 to 4 years (12-15). Although in these studies no effect of iv AAT on decline of FEV$_1$ could be proven, it was presumed that iv AAT treatment effect on lung densitometry was preceding protection of change in FEV$_1$ later in time. This implies that the follow-up time in these randomized controlled trials was too short to measure a difference between the placebo and AAT-treated group with respect to FEV$_1$ decline. Alternatively, it suggests that the study population was too small to detect a treatment effect especially as in many patients deterioration of FEV$_1$ can stabilize in some patients after cessation of smoking, which is a recognised driver of emphysema progression and smokers have always been excluded from such trials (16).

The aim of the current study was to determine whether long-term iv AAT augmentation therapy preserves decline in FEV$_1$ compared to cohorts where such therapy has been unavailable.

**Methods**

**Study design and patients**

To stimulate the availability of long-term follow-up data and appropriate research, the World Health Organization (WHO) advised the establishment of an international registry for AATD in 1997, and the Alpha-1 International Registry (AIR) was founded (17). In this registry, patients’ data were collected by members of AIR and stored in a common database. The members were dedicated clinical scientists who entered baseline and follow up data of AATD patients, as described in detail previously (18). All patients included in AIR had signed written informed consent for the anonymous use of their data for research, prior to entering data into the registry (19).

In the current study, we analysed AIR data from five different countries: the Netherlands, Germany, Italy, the United Kingdom and Spain, as those countries had the most complete datasets.

**Procedures**

To assess the effect of AAT augmentation treatment over a longer-term, data from patients with
FEV\textsubscript{1} values collected over more than four years were extracted from the AIR database. These data were used in this retrospective cohort study of international longitudinal data of individual ZZ-AATD patients. Data registered up until January 1, 2014 were used. The individuals were selected based on the following inclusion criteria: age > 25 years, phenotype ZZ-AATD, availability of ≥ four years of follow-up data, and a baseline (at the moment of entering AIR) post-bronchodilator FEV\textsubscript{1} value between 30% and 65% predicted. Patients were excluded when there were missing data on the key variables: date of birth, sex, length, smoking status, phenotype and AAT therapy status. Also, patients who received a lung transplant, current smokers or those who stopped smoking less than six months before the start of AAT treatment were excluded. Additionally, only patients on treatment located in countries where there is augmentation therapy available and reimbursed (Spain, Germany and Italy) were included in the treatment group. Patients without treatment located in countries where there is no augmentation therapy available and reimbursed (the Netherlands and the United Kingdom) were included in the untreated group.

Outcomes

The post-bronchodilator FEV\textsubscript{1} %predicted values for baseline and each follow-up moment were calculated for each patient from the absolute FEV\textsubscript{1} values in liters using the GLI standard correction (20). Additionally, the course of FEV\textsubscript{1} in L of both groups were also compared. Based on the GOLD-COPD guideline, optimal bronchodilator treatment for patients was taken as the use of long-acting bronchodilators (3). Therefore, missing follow-up values not formally stated as post-bronchodilator FEV\textsubscript{1} were taken as the FEV\textsubscript{1} values on prescribed bronchodilator therapy as documented in the AIR database.

Statistical analysis

Data was stratified by country, categorical variables were reported as numbers and percentages, continuous variables as means with standard deviations. Linear mixed effects models were used to
determine the annual decline in ‘post-bronchodilator’ FEV\textsubscript{1} values of the two groups of ZZ-AATD patients, those with and without augmentation therapy.

For the linear mixed effects models, “post-bronchodilator” FEV\textsubscript{1} at the different timepoints is the dependent variable, and as fixed effects we used treatment modality, follow-up duration and the interaction between follow-up duration and treatment, sex, age at follow-up moment and packyears of previous smoking. To model the within-patient correlation we used random intercepts and slopes terms. To determine if therapy has an effect on the decline of FEV\textsubscript{1}, the likelihood ratio test was used (21). A likelihood-ratio test result with a difference of a \emph{p}-value < 0.05 was considered significant. Statistical analyses were performed using IBM SPSS statistics version 26 for windows. A more comprehensive description of the Linear Mixed Effects Models is documented in supplementary material paragraph 1.1.

Results
Study population and baseline characteristics
For the current study, a total of 3248 registered patients from the United Kingdom, the Netherlands, Germany, Italy and Spain were identified in the AIR database. Based on missing data or exclusion criteria, 2821 patients were excluded from subsequent analysis. Additionally, we identified 48 patients who were eligible for augmentation therapy in their country but were not treated for undocumented reasons and therefore were also excluded from the analysis. A total of 374 patients remained for the linear mixed effects model analysis, 246 patients were included in the group with no augmentation therapy (controls) and 128 patients in the group with AAT augmentation treatment. Figure 1 shows the flow-chart of the in- and exclusion criteria of the study individuals per country.

A total of 2268 FEV\textsubscript{1} values were analysed, with an average of 6.1 annual FEV\textsubscript{1} values per ZZ-AATD patient. All baseline FEV\textsubscript{1} values were documented post-bronchodilator values. However, 180 (7.9\%) follow-up post-bronchodilator values were not documented or formally assessed and therefore were
replaced by ‘formal pre-bronchodilator FEV₁’ values from 113 ZZ-AATD patients documented in the database as on usual daily bronchodilator therapy. The mean follow-up duration in the untreated group was 8.60 years (SD ± 3.34) and 8.59 (± 2.62) in the treated group. The baseline characteristics are summarised in table 1.

**Linear mixed effects model analysis**

The mean annual decline in FEV₁ %predicted in the treated and untreated group were calculated by applying a linear mixed effects model analysis. The best fitted mixed model analysis showed a mean FEV₁ decline of -0.931 % predicted per year (95% confidence interval -1.144 to -0.718) in the untreated group, and -1.016% predicted per year (-1.319 to -0.7145) in the treated group, as summarised in Figure 2. The likelihood ratio test showed no difference between the two groups (P = 0.71).

The mixed model analysis of the FEV₁ decline in liters also showed no difference between the two groups, *this analysis is documented in supplementary material, paragraph 1.2 and 2.2.*

**Discussion**

This retrospective analysis of European real-world follow-up data of the decline in FEV₁ %predicted in ZZ-AATD patients showed no difference in annual FEV₁ decline between the AAT augmentation treated and untreated patients over a period of more than 8 years. The mean decline of FEV₁ in ZZ-AATD patients was best expressed as the % predicted to account for the natural aging decline and normalise data between subject for sex and height.

The annual FEV₁ decline reported in our long-term study is less than that reported in the most recently performed short-term randomized control trial for AAT augmentation therapy, the RAPID study (13). That study also showed no difference in FEV₁ decline (P = 0.21) between groups. Indeed, FEV₁ decline was (mean ±SD) -2.3% ± 13.1% predicted over two years in the placebo group and -3.1% ± 10.7% predicted in the treated group [13]. Whereas the shorter period of follow up in the RAPID
trial may have affected the detection of any difference in decline rate of FEV$_1$, our longer-term
follow-up study has not provided support of the statement in the RAPID-OLE manuscript, that lung
density change in favour of iv AAT augmentation treatment will eventually be reflected in a reduced
FEV$_1$ decline in the longer term [14].

The results of our study also support the findings of previous limited analyses of ZZ-AATD patients.
The national German registry analysis with patients who had not received augmentation therapy (N= 15) and patients who did receive therapy (N= 85) over a mean follow-up of 4.89 years (22) showed
no difference in FEV$_1$ decline between groups. Neither did the analysis of the Spanish national
database of patients who did not receive augmentation therapy (N= 45) and patients who did receive augmentation therapy (N= 77) over an average of more than eight years (23).

Our database study has some important strengths. First, in this study data from five different
countries are combined to form the two groups of interest. The use of data from an international
registry of a rare disease makes it possible to analyse data of a higher number of ZZ-AATD patients
and creates the opportunity to combine data from countries where there is no augmentation
therapy available with data from countries where AAT augmentation therapy is both available and
reimbursed. Second, most included patients had multiple follow-up FEV$_1$ values over a mean follow-
up time of more than eight years with an average of 6.1 FEV$_1$ values for slope analysis. These two
factors increase the accuracy of the presented mean of both groups in our study (24). Third,
selection bias for inclusion of patients in our study was limited using the ATS/ERS statement for
diagnosis and treatment of individuals with AATD [7]. Another strength of our analysis is that in our
study FEV$_1$ decline is primarily expressed in %predicted instead of L/year, to account for a corrected
value for the age-related decline of FEV$_1$ (16).

There are also some limitations of our study. First, most data were added retrospectively from paper
files into the registry. Unfortunately, this resulted in some missing data, even following two requests
for data from contributors checking their source data, and thereby led to a high number of excluded
patients which might have led to inadvertent selection bias and marked reduction in patient number fulfilling all the inclusion criteria. Second, over the years the iv AAT dosing regimen in the 3 countries has been variable and occasionally interrupted for some months due to drug supply problems. This break in therapy was not carefully documented in the registry. Third, in this study the choice for analysing the post-bronchodilator FEV₁ instead of the pre-bronchodilator FEV₁ values was based on the ATS/ERS guideline for the analysis of follow-up FEV₁ in chronic obstructive pulmonary disease (COPD) (25). This guideline does not state about the formality or use of the type or dose of bronchodilator, i.e. short-acting β2-agonist or short-acting muscarinic antagonist. In the AIR database no data was collected about the type of bronchodilator used for the measurement of the post-bronchodilator FEV₁ values. Also, the registry does not include data about the use and timing of long-acting bronchodilators on the day of the spirometry. Fourth, several other factors are known to influence FEV₁ decline in AATD: baseline FEV₁, smoking history, age, BMI and exacerbation rate (22, 26). In our database, no exacerbation rate or respiratory symptoms are registered, apart from the St. George’s Respiratory Questionnaire score at baseline. Values of BMI and exacerbation rates were often missing in the follow up database. However, the other known influencing factors on FEV₁ decline, i.e. previous smoking history and patient age were applied as confounders in the mixed models. Although smoking has a major effect on FEV₁ decline it should be noted that all patients on augmentation had to have stopped smoking, which in its own right would likely reduce subsequent decline (16). The time from quitting smoking to the date of starting augmentation treatment (the period of being ex-smoker) could not be used as a confounder in the mixed effects model. By doing so, we were unable to model the never-smokers without creating another and smaller subgroup analysis. Therefore, we only applied the number of packyears in our mixed models.

Even though the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) guidance for new drug studies in COPD have determined that the FEV₁ should be the primary outcome in drug development (27), the findings in our study suggest that FEV₁ decline would be inappropriate to evaluate the effect of AAT augmentation therapy in ZZ-AATD patients.
Historically, AAT augmentation therapy with a dose of 60 mg/kg has been introduced based on the hypothetical effect on reducing FEV\textsubscript{1} decline by restoring the protease-antiprotease balance through AAT substitution. Indeed limited studies of airways secretions indicate both a rise in local AAT levels and a reduction in protease activity consistent with this concept (28). More recent studies also indicate that excess protease activity is present in the lung (29), albeit not specific for the lung (30, 31). These biomarkers or footprints of excess protease activity might be useful to perform dose-ranging studies of AAT augmentation therapy to evaluate the effect on the protease balance and whether the current dose of 60 mg/kg is sufficient for an individual patient as intimated by Campos et al (32).

However, other molecular mechanisms affected by the ZZ-AATD phenotype may also be responsible for emphysema development such as quantitative and qualitative properties of circulating Z-AAT polymers, dysregulation of immune cell responses and endothelial cell function or generation of unknown pro-inflammatory substances (33).

Finally, it should be re-emphasised that the FEV\textsubscript{1} is a poor surrogate for the emphysema process and far less sensitive to change than lung densitometry. In addition, decline in FEV\textsubscript{1} is both variable in AATD and even stabilises (other than normal age-related decline) in a proportion of ex-smokers. Studies of patients not documented for rapid decline post smoking will include a variable portion of patients who stabilize and reduce the power for using FEV\textsubscript{1} as an outcome parameter thus requiring large numbers of subjects to identify statistical differences as in the NHLBI study (5) and in the meta-analysis by Chapman et al (8). To support development of new outcome parameters for research in AATD, the EARCO initiative was established together with the European Respiratory Society (34). A protocol was developed to assess complete phenotyping of AATD patients (www.earco.org).

We conclude that our “real-world data” could not show a difference in long-term annual FEV\textsubscript{1} decline in ZZ-AATD patients who received intravenous AAT augmentation treatment for emphysema compared to those who did not. Other approaches are needed to validate any benefits of iv
augmentation therapy or determine reasons other than number, current status and length of study required to be confident of the benefits of such therapy.

**Acknowledgements**

We thank Prof. S. Janciauskiene, Department of Pulmonology, Hannover Medical School for critical reading of the manuscript.
References


Table 1 patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>UK</th>
<th>Italy</th>
<th>Germany</th>
<th>Spain</th>
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<tbody>
<tr>
<td></td>
<td>Not treated</td>
<td>Not treated</td>
<td>Treated</td>
<td>Treated</td>
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<tr>
<td>N</td>
<td>59</td>
<td>187</td>
<td>n=3</td>
<td>n=116</td>
<td>n=9</td>
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<tr>
<td>Male gender, n (%)</td>
<td>33 (55.9)</td>
<td>119 (63.6)</td>
<td>1 (33.3)</td>
<td>76 (65.5)</td>
<td>6 (66.7)</td>
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<td>Age at baseline in years, mean (SD)</td>
<td>46.7 (7.6)</td>
<td>52.3 (8.7)</td>
<td>61.0 (6.0)</td>
<td>53.4 (9.7)</td>
<td>53.0 (4.8)</td>
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<td>Smoking status</td>
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<td>Never, n (%)</td>
<td>4 (6.8)</td>
<td>28 (15.0)</td>
<td>1 (33.3)</td>
<td>26 (22.4)</td>
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<td>Former, n (%)</td>
<td>55 (93.2)</td>
<td>159 (85.0)</td>
<td>2 (66.7)</td>
<td>90 (77.6)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Packyears (SD)</td>
<td>17.2 (10.1)</td>
<td>20.7 (21.3)</td>
<td>15 (15)</td>
<td>15.4 (12.5)</td>
<td>17.3 (5.3)</td>
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<tr>
<td>Baseline FEV₁ % pred (SD)</td>
<td>47.3 (9.1)</td>
<td>46.4 (9.6)</td>
<td>37.3 (4.9)</td>
<td>46.2 (10.1)</td>
<td>47.2 (7.7)</td>
</tr>
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Abbreviation: SD= standard deviation, FEV₁ %pred= post bronchodilator forced expiration in 1 second express as percentage predicted
When all the exclusion criteria were applied, the total number of excluded subjects was the number shown in the box. The bottom box shows the subjects who are included in the linear mixed effects model analysis. Exclusion based on missing data of key variables: date of birth, sex, length, smoking status, phenotype, AAT therapy status. Exclusion criteria: age < 25 years, phenotype not ZZ-AATD, follow-up data < four years, baseline post-bronchodilator FEV1%pred value < 30 % or >65% predicted, lung transplantation, current smokers, stopped smoking ≤ six months prior to inclusion. Abbreviation: AAT= alpha-1-antitrypsin, FEV1 %pred= forced expiration in 1 second express as percentage predicted for age, sex and height.
The figure shows the decline in FEV1 % predicted over the years calculated by the mixed model without confounders, for both groups; untreated and treated. The confidence interval (CI) of both graphs are overlapping, thereby only the upper CI of the treated graph and the lower CI of the untreated graph is shown. There was no significant difference in decline in FEV1. Abbreviation: FEV1%pred, post bronchodilator forced expired volume in 1 second express as percentage predicted.
Supplementary material

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   2.2 Results Linear Mixed Effects Models FEV₁ in Liters
1. Method

1.1 Comprehensive description Linear Mixed Effects Model of FEV₁ in %predicted

This description includes the steps that are taken to formulate the final linear mixed effects model. Different models were generated and compared to each other. The models were fitted using the Restricted Maximum Likelihood (REML) approach. Based on the Akaike Information Criteria (AIC) the final and best fitted model for the data was stepwise selected by including one confounding factor at each step. The selection of the included cases is described in the method section of the main text.

In the first linear mixed effects model, the post-bronchodilator FEV₁ %predicted was the dependent variable and modeled by treatment modality, with follow-up duration, sex, age at follow-up moments and packyears. In the model, treatment modality, sex, age at follow-up moments, packyears, follow-up duration, the interaction between treatment modality and follow-up duration, follow-up duration as quadratic factor, and the interaction between treatment modality and follow-up duration as quadratic factor were added as fixed effects. As random effect, the intercept of the subjects and follow-up duration were added. Follow-up duration was also added as repeated effect. The first model showed an AIC of 15960.587.

In the second mixed model the same variables were added but follow-up duration was also added as a random effect. This model showed an AIC of 15174.570. Based on this value the decision was made to continue with the second model.

In the third model correlation within countries was added as a confounder, as patients within a country are likely be more homogenous. Country was thereby added as random and repeated effect besides follow-up duration. This model showed an AIC of 15176.426. Because of the small difference in AIC compared to the second model, a chi-squared test was performed based on the log Likelihood, showing no difference between model 2 and 3 (P=0.70). Therefore, the less complicated model 2; without the correlation within countries, was chosen as the best fit model for continuation.

For the fourth and final model, follow-up duration as quadratic factor, and the interaction between follow-up duration and treatment modality were excluded as fixed variable. This model showed an AIC of 15179.733. Again because of the small difference in AIC compared to the second model, a chi-squared test was performed on the log Likelihood, which showed no difference between model 2 and 4 (P=0.16). Model 4 was even less complicated and thus was used as the best fit model for continuation.

To test the effect of therapy, model four was applied for both the augmentation treatment and non-treatment group. Because both were compared to each other, these models were fitted to the
maximum likelihood (ML) instead of the restricted maximum likelihood (REML). The log Likelihood of both models was tested with the chi-squared test to assess any difference in FEV₁ decline between both groups. This test showed no difference between the groups (P=0.71).

1.2 Description of the Linear Mixed Effects Models of FEV₁ in Liters

This description includes the steps which are taken to formulate the final linear mixed effects model for the FEV₁ in Liters (L). The different models were generated with the same methodology as for the FEV₁ %predicted, but a different final model was considered the best fit.

In the first linear mixed effects model, the post-bronchodilator FEV₁ in L was the dependent variable and modeled by treatment modality with follow-up duration, sex, age at follow-up moments and packyears. In the model, treatment modality, sex, age at follow-up moments, packyears, follow-up duration, the interaction between treatment modality and follow-up duration, follow-up duration as quadratic factor, and the interaction between treatment modality and follow-up duration as quadratic factor were added as fixed effects. As random effect the intercept of the subjects and follow-up duration were added. Follow-up duration was also added as repeated effect. The first model showed an AIC of 381.122.

In the second mixed model, the same variables were added but follow-up duration was also added as a random effect. This model showed an AIC of -316.177. Based on these values the decision was made to continue with the second model.

In the third model correlation within countries was added as a confounder as patients within a country are likely be more homogenous. Country was thereby added as random and repeated effect besides follow-up duration. This model showed an AIC of -322.408. Because of the small difference in AIC compared to the second model, a chi-squared test was performed on the log likelihood, which showed a significant difference between model 2 and 3 (P=0.00). Therefore, the model with the best AIC, model 3 was the chosen for continuation.

For the fourth and final model, follow-up duration as quadratic factor, and the interaction between follow-up duration and treatment modality were excluded as fixed variable. This model showed an AIC of -328.562. Because of the small difference in AIC compared to the third model, a chi-squared test was performed which showed a significant difference between model 3 and 4 (P=0.05). Model 4 was less complicated and therefore used for continuation.
To test the effect of therapy, model four was applied for both the augmentation treatment and non-augmentation treatment group. Because both models were compared to each other, they were fitted to the maximum likelihood (ML) instead of the restricted maximum likelihood (REML). The log likelihood of both models were tested by the chi-squared test to assess any difference in FEV₁ decline between groups. This test showed no difference between the two groups (P=0.67).
2. Results

2.1 Graph Linear Mixed Effects Models FEV\textsubscript{1} %predicted

Figure S1. Graph FEV\textsubscript{1} decline in %predicted

Notes: The figure shows the decline in FEV\textsubscript{1} in percentage predicted over the years calculated by the mixed model without confounders, for both groups; untreated and treated.

Abbreviation: FEV\textsubscript{1} = post bronchodilator forced expiration in 1 second express as percentage, AAT = Alpha-1-antitrypsin
2.2 Results Linear Mixed Effects Models FEV\textsubscript{1} in Liters

Baseline FEV\textsubscript{1} values in liters of all the subjects are summarized in *table S1*. For the additional baseline characteristics see *table 1* in the main text. In the linear mixed effect model analysis only the patients who received augmentation treatment in a country where treatment is available and reimbursed are included in the treatment group and patients who did not receive augmentation treatment from countries where treatment is not available and reimbursed are included in the control group. The mean annual decline in FEV\textsubscript{1} for each group was calculated by applying a mixed model analysis for each group.

Different mixed models were tested based on the likelihood ratio test to define the fixed and random parameters. For the linear mixed effects models, “post-bronchodilator” FEV\textsubscript{1} in liters at the different timepoints is the dependent variable, and as fixed effects we used treatment modality, follow-up duration and the interaction between follow-up duration and treatment, sex, age at follow-up time and packyears of previous smoking. To model the within-patient correlation we used random intercepts and slopes terms. Country was added as a random effect besides follow-up duration.

The best fit mixed model analysis showed a mean FEV\textsubscript{1} decline of -0.0291 L per year (95% confidence interval -0.0360 to -0.0223) in the control group and compared to a mean FEV\textsubscript{1} decline of -0.0339 L per year (95% CI -0.0434 to -0.02432) in the augmentation treatment group. The likelihood ratio test showed no difference between the two groups (P=0.67). *See figure S2.*

**Table S1. Baseline FEV\textsubscript{1} in liters, stratified per country**

<table>
<thead>
<tr>
<th>Country</th>
<th>The Netherlands</th>
<th>UK</th>
<th>Italy</th>
<th>Germany</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not treated</td>
<td>Not treated N = 59</td>
<td>Not treated N = 187</td>
<td>Treated N=3</td>
<td>Treated N = 116</td>
<td>Treated N = 9</td>
</tr>
<tr>
<td>Baseline FEV\textsubscript{1} L (SD)</td>
<td>1.65 (0.39)</td>
<td>1.46 (0.40)</td>
<td>0.90 (0.15)</td>
<td>1.50 (0.42)</td>
<td>1.45 (0.41)</td>
</tr>
</tbody>
</table>

*Abbreviation: SD = standard deviation, FEV\textsubscript{1} L = post bronchodilator forced expiration in 1 second in liters*
The figure shows the decline of FEV$_1$ in liters over the years calculated by the mixed model without confounders, for both groups; untreated and treated. The confidence interval (CI) of both graphs are overlapping, thereby only the upper CI of the untreated graph and the lower CI of the treated graph is shown. There was no significant difference in decline in FEV$_1$. 

**Notes:** The figure shows the decline of FEV$_1$ in liters over the years calculated by the mixed model without confounders, for both groups; untreated and treated. The confidence interval (CI) of both graphs are overlapping, thereby only the upper CI of the untreated graph and the lower CI of the treated graph is shown. There was no significant difference in decline in FEV$_1$. 

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**Figure S2. FEV$_1$ decline in Liters**

![Graph showing FEV$_1$ decline over years for untreated and treated groups](image-url)
Figure S3. FEV₁ decline in Liters

Notes: The figure shows the decline in FEV₁ in liters over the years calculated by the mixed model without confounders, for both groups; untreated and treated.