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# Long-term effect of $\alpha_1$ -antitrypsin augmentation therapy on the decline of FEV<sub>1</sub> in deficient patients: an analysis of the AIR database

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This analysis of European real-world follow-up data of FEV<sub>1</sub> % predicted in ZZ  $\alpha_1$ -ATD patients showed no difference in annual FEV<sub>1</sub> decline between the *i.v.*  $\alpha_1$ -AT augmentation treated and untreated patients over a period of >8 years <https://bit.ly/35MglRc>

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## Abstract

**Background** Patients with ZZ (Glu342Lys)  $\alpha_1$ -antitrypsin deficiency (ZZ-AATD) who received augmentation therapy with  $\alpha_1$ -antitrypsin (AAT) in randomised controlled trials over 2–3 years failed to show a significant reduction of the annual decline of forced expiratory volume in 1 s (FEV<sub>1</sub>).

**Methods** To compare the trajectory of FEV<sub>1</sub> change during 4 or more years in ZZ-AATD patients with emphysema receiving or not receiving intravenous augmentation therapy, a retrospective analysis of FEV<sub>1</sub> 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 FEV<sub>1</sub> % 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 $\pm$ SD follow-up duration of the untreated group was 8.60 $\pm$ 3.34 years and 8.59 $\pm$ 2.62 years for the treated group. The mixed effects model analysis showed a mean FEV<sub>1</sub> decline of –0.931% predicted per year (95% CI –1.144 to –0.718) in the untreated group and a decline of –1.016% predicted per year (95% CI –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 FEV<sub>1</sub> by AAT augmentation treatment over a mean 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 1 s (FEV<sub>1</sub>) 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<sub>1</sub> have a poorer prognosis, as a lower FEV<sub>1</sub> is a predictor for all-cause and respiratory mortality [3–5].

More than 25 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 American Thoracic Society (ATS)/European Respiratory Society (ERS) statement recommends weekly AAT augmentation therapy with 60 mg·kg<sup>-1</sup> body weight for AATD patients with AAT serum levels below the putative protective threshold of 11.0 μM and an FEV<sub>1</sub> 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<sub>1</sub> in ZZ-AATD patients who received AAT augmentation treatment compared to those who did not.

The rate of the annual FEV<sub>1</sub> 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<sub>1</sub> [11]. Based on this validation, lung densitometry has been used as the outcome parameter in several placebo-controlled randomised clinical trials to determine the effect of intravenous (*i.v.*) AAT augmentation treatment on preservation of lung tissue. A consistent protective effect of *i.v.* 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 *i.v.* AAT on decline of FEV<sub>1</sub> could be proven, it was presumed that *i.v.* AAT treatment effect on lung densitometry was preceding protection of change in FEV<sub>1</sub> later in time. This implies that the follow-up time in these randomised controlled trials was too short to measure a difference between the placebo and AAT-treated group with respect to FEV<sub>1</sub> decline. Alternatively, it suggests that the study population was too small to detect a treatment effect especially as in many patients deterioration of FEV<sub>1</sub> can stabilise 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 *i.v.* AAT augmentation therapy preserves decline in FEV<sub>1</sub> 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<sub>1</sub> values collected over > 4 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 ≥4 years of follow-up data, and a baseline (at the moment of entering AIR) post-bronchodilator FEV<sub>1</sub> value between 30% and 65% predicted. Patients were excluded when there were missing data on the key variables: date of birth, sex, height, smoking status, phenotype and AAT therapy status. Also, patients who received a lung transplant, current smokers or those who stopped smoking <6 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<sub>1</sub>% predicted values for baseline and each follow-up moment were calculated for each patient from the absolute FEV<sub>1</sub> values in litres using the Global Lung Initiative (GLI) standard correction [20]. Additionally, the course of FEV<sub>1</sub> in L of both groups were also compared. Based on the Global Initiative for Chronic Obstructive Lung Disease (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<sub>1</sub> were taken as the FEV<sub>1</sub> 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 mean±SD. Linear mixed effects models were used to determine the annual decline in “post-bronchodilator” FEV<sub>1</sub> values of the two groups of ZZ-AATD patients, those with and without augmentation therapy.

For the linear mixed effects models, “post-bronchodilator” FEV<sub>1</sub> 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 pack-years 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<sub>1</sub>, the likelihood ratio test was used [21]. A likelihood ratio test result with a difference of a p-value <0.05 was considered significant. Statistical analyses were performed using IBM SPSS statistics version 26 for Windows (IBM, Chicago, IL, USA). 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 inclusion and exclusion criteria of the study individuals per country.

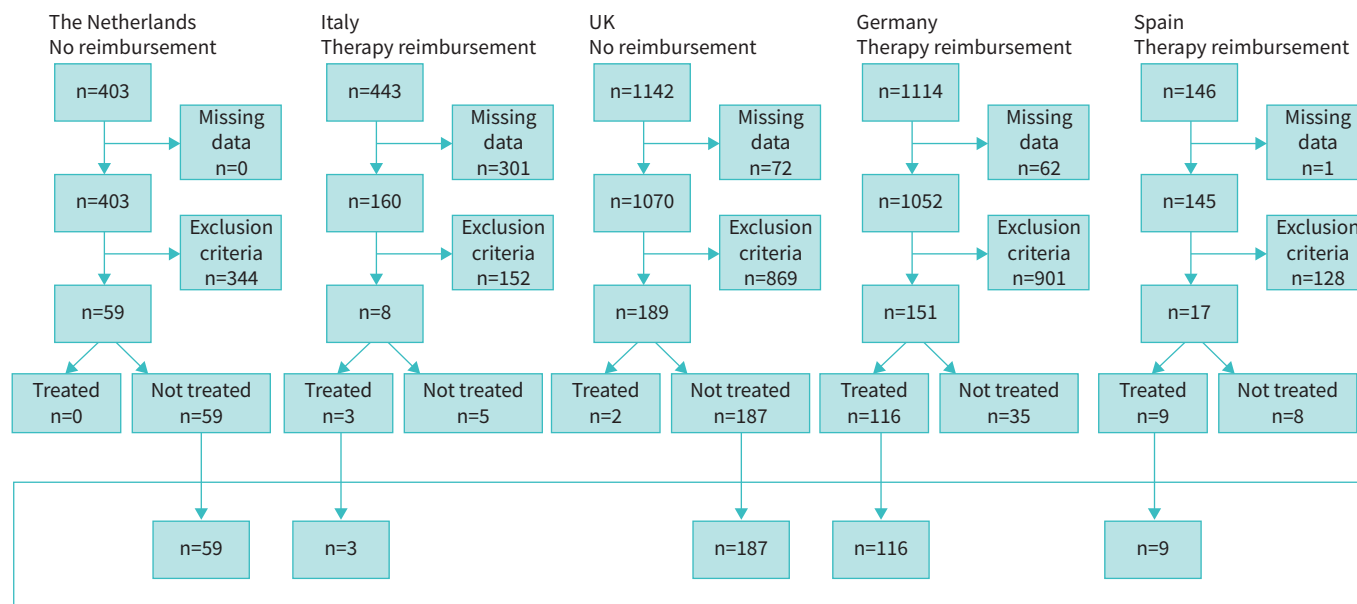
A total of 2268 FEV<sub>1</sub> values were analysed, with a mean of 6.1 annual FEV<sub>1</sub> values per ZZ-AATD patient. All baseline FEV<sub>1</sub> values were documented post-bronchodilator values. However, 180 (7.9%) follow-up post-bronchodilator values were not documented or formally assessed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

### Linear mixed effects model analysis

The mean annual decline in FEV<sub>1</sub> % predicted in the treated and untreated group was calculated by applying a linear mixed effects model analysis. The best fitted mixed model analysis showed a mean FEV<sub>1</sub> 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 FEV<sub>1</sub> decline in litres also showed no difference between the two groups (this analysis is documented in the supplementary material, paragraphs 1.2 and 2.2).

## Discussion

This retrospective analysis of European real-world follow-up data of the decline in FEV<sub>1</sub> % predicted in ZZ-AATD patients showed no difference in annual FEV<sub>1</sub> decline between the AAT augmentation treated and untreated patients over a period of >8 years. The mean decline of FEV<sub>1</sub> in ZZ-AATD patients was best expressed as the % predicted to account for the natural ageing decline and normalise data between subjects for sex and height.



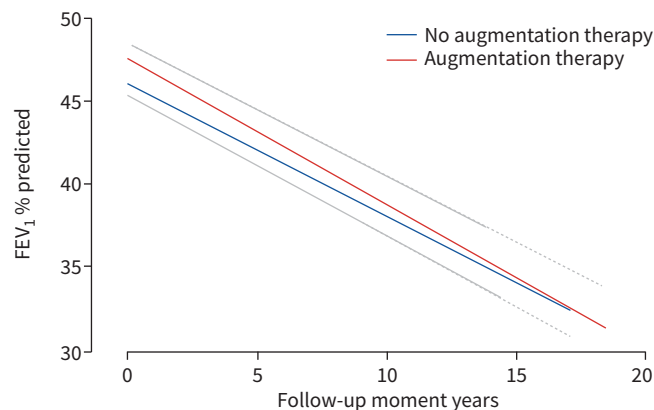
**FIGURE 1** When all the exclusion criteria were applied, the total number of excluded subjects is the number shown in the box. The bottom box shows the subjects who are included in the linear mixed effects model analysis. Exclusion based on missing data of key variables: date of birth, sex, length, smoking status, phenotype,  $\alpha$ -1-antitrypsin (AAT) therapy status. Exclusion criteria: age <25 years, phenotype not ZZ (Glu342Lys)  $\alpha$ -1-antitrypsin deficiency (ZZ-AATD), follow-up data <4 years, baseline post-bronchodilator FEV<sub>1</sub> % predicted value <30% or >65% predicted, lung transplantation, current smokers, stopped smoking  $\leq$ 6 months prior to inclusion.

The annual FEV<sub>1</sub> decline reported in our long-term study is less than that reported in the most recently performed short-term randomised controlled trial for AAT augmentation therapy, the RAPID study [13]. That study also showed no difference in FEV<sub>1</sub> decline (p=0.21) between groups. Indeed, mean $\pm$ SD FEV<sub>1</sub> decline was  $-2.3\pm 13.1\%$  predicted over 2 years in the placebo group and  $-3.1\pm 10.7\%$  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<sub>1</sub>, our longer-term follow-up study has not provided support of the statement in the RAPID-OLE study [14], that lung density change in favour of *i.v.* AAT augmentation treatment will eventually be reflected in a reduced FEV<sub>1</sub> decline in the longer term.

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<sub>1</sub> 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 >8 years [23].

	The Netherlands	UK	Italy	Germany	Spain
<b>Treated/not treated n</b>	Not treated 59	Not treated 187	Treated 3	Treated 116	Treated 9
<b>Male sex, n (%)</b>	33 (55.9)	119 (63.6)	1 (33.3)	76 (65.5)	6 (66.7)
<b>Age at baseline years</b>	46.7 $\pm$ 7.6	52.3 $\pm$ 8.7	61.0 $\pm$ 6.0	53.4 $\pm$ 9.7	53.0 $\pm$ 4.8
<b>Smoking status</b>					
Never, n (%)	4 (6.8)	28 (15.0)	1 (33.3)	26 (22.4)	0 (0)
Former, n (%)	55 (93.2)	159 (85.0)	2 (66.7)	90 (77.6)	9(100)
Pack-years	17.2 $\pm$ 10.1	20.7 $\pm$ 21.3	15 $\pm$ 15	15.4 $\pm$ 12.5	17.3 $\pm$ 5.3
<b>Baseline FEV<sub>1</sub> % pred</b>	47.3 $\pm$ 9.1	46.4 $\pm$ 9.6	37.3 $\pm$ 4.9	46.2 $\pm$ 10.1	47.2 $\pm$ 7.7

Data expressed as mean $\pm$ SD unless otherwise indicated. FEV<sub>1</sub>: forced expiratory volume in 1 s.



**FIGURE 2** Decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) as % predicted over the years calculated by the mixed model without confounders, for both groups: untreated and treated. The confidence intervals of both graphs are overlapping, thereby only the upper confidence interval of the treated graph and the lower confidence interval of the untreated graph is shown. There was no significant difference in decline in FEV<sub>1</sub>.

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<sub>1</sub> values over a mean follow-up time of >8 years with a mean of 6.1 FEV<sub>1</sub> 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<sub>1</sub> decline is primarily expressed in % predicted instead of litres per year, to account for a corrected value for the age-related decline of FEV<sub>1</sub> [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 a marked reduction in patient number fulfilling all the inclusion criteria. Second, over the years the *i.v.* AAT dosing regimen in the three 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 FEV<sub>1</sub> instead of the pre-bronchodilator FEV<sub>1</sub> values was based on the ATS/ERS guideline for the analysis of follow-up FEV<sub>1</sub> in COPD [25]. This guideline does not state about the formality or use of the type or dose of bronchodilator, *i.e.* short-acting  $\beta_2$ -agonist or short-acting muscarinic antagonist. In the AIR database no data were collected about the type of bronchodilator used for the measurement of the post-bronchodilator FEV<sub>1</sub> 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 FEV<sub>1</sub> decline in AATD: baseline FEV<sub>1</sub>, smoking history, age, body mass index (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 FEV<sub>1</sub> decline, *i.e.* previous smoking history and patient age, were applied as confounders in the mixed models. Although smoking has a major effect on FEV<sub>1</sub> 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 an 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 pack-years 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 FEV<sub>1</sub> should be the primary

outcome in drug development [27], the findings in our study suggest that FEV<sub>1</sub> 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<sup>-1</sup> has been introduced based on the hypothetical effect on reducing FEV<sub>1</sub> decline by restoring the protease–antiprotease balance through AAT substitution. Indeed limited studies of airway 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<sup>-1</sup> 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<sub>1</sub> is a poor surrogate for the emphysema process and far less sensitive to change than lung densitometry. In addition, decline in FEV<sub>1</sub> 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 stabilise and reduce the power for using FEV<sub>1</sub> 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](http://www.earco.org)).

We conclude that our “real-world data” could not show a difference in long-term annual FEV<sub>1</sub> 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 *i.v.* augmentation therapy or determine reasons other than number, current status and length of study required to be confident of the benefits of such therapy.

Submitted article, peer reviewed.

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