ICS Use May Modify FEV₁ Decline in α_1 -Antitrypsin Deficiency Patients with Relatively High Blood Eosinophils

Emma V. Low^a Siân M. Hughes^b Safia Zaffarullah^a Dimitris Kantas^c
Robert Andrew Stockley^b Alice M. Turner^d

^aHeart of England NHS Foundation Trust, Birmingham, UK; ^bQueen Elizabeth Hospital, Birmingham, UK;
^cUniversity Hospital of Ioannina, Ioannina, Greece; ^dInstitute of Inflammation and Ageing, University of Birmingham, Birmingham, UK

Keywords

α_1 -Antitrypsin deficiency · Chronic obstructive pulmonary disease · Eosinophils · Respiratory function tests · Survival · Inhaled corticosteroids

Abstract

Background: α_1 -Antitrypsin deficiency (AATD) predisposes to chronic obstructive pulmonary disease (COPD). In COPD unrelated to AATD, the role of a higher blood eosinophil count in disease and subsequent personalization of therapy has recently received much attention. We sought to investigate this concept in patients with AATD-associated COPD. **Objectives:** The study aims to evaluate eosinophilia status against outcomes including mortality and FEV₁ decline in patients with AATD. **Methods:** All patients with PiSZ and PiZZ genotypes were identified from the UK AATD registry. The participants were substratified according to inhaled corticosteroid (ICS) use. Blood eosinophil counts were assessed from baseline and annually during follow-up (range 1–18 years). Eosinophilia was defined as a level $>0.2 \times 10^9/L$, and classified by the frequency of such counts into “always,” “intermittent,” or “never present.” Univariate and multivariate analyses were conducted. **Results:** In total, 646 participants

were included, 53.9% of whom demonstrated intermittent and 7.4% persistent eosinophilia. Survival did not differ according to eosinophilic group ($p > 0.05$). Those with persistent eosinophilia showed a slower FEV₁ decline ($p < 0.001$). There was no clear association with exacerbation frequency. Patients on ICS at baseline were more likely to be eosinophilic ($p = 0.002$) and having a lower FEV₁ ($p < 0.001$) and greater pack-year exposure (16.5 vs. 7.8 pack-years, $p < 0.001$). When the multivariate analyses of FEV₁ decline were stratified for baseline ICS use, the association of persistent eosinophilia with slower decline persisted in those on ICS. **Conclusions:** Blood eosinophil levels persistently $>0.2 \times 10^9/L$ may be an indication for ICS use in PiZZ AATD in order to reduce FEV₁ decline.

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Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 64 million people worldwide, carries significant morbidity for those affected, and is predicted to be the third leading cause of death worldwide by 2030 [1]. Although the pathogenesis of COPD is not wholly

understood, the overarching concept is a neutrophilic inflammatory process causing a progressive destruction of lung tissue [2]. A number of subphenotypes have been identified and can be used to direct specific therapies [3], and some phenotypes demonstrate discrete biochemical and clinical profiles. α_1 -Antitrypsin is a neutrophil elastase inhibitor, and in α_1 -antitrypsin deficiency (AATD) there is a poorly controlled release of elastases resulting in destruction of elastin in the lung tissue, a process mainly associated with the development of emphysema [4]. AATD is a hereditary disorder which predisposes to COPD [4]. There are a number of AATD genotypes which demonstrate clinical heterogeneity; PiZZ and PiSZ are the most commonly reported, with the PiSZ form being closer to non-AATD COPD in appearance than the PiZZ form [5].

Non-AATD COPD is typically associated with T-helper 1 lymphocyte-mediated immunity and involves neutrophilic inflammation. Eosinophilic inflammation is classically associated with allergic sensitization and airway inflammation in asthma [6]. However, a number of studies have confirmed that 20–40% of COPD patients also demonstrate eosinophilic airway inflammation [7–11]. Mature circulating blood eosinophils are recruited into the airways by immunoregulatory cells and chemokines. Eosinophils have been described as having an immunomodulatory role in airway disease. They synthesize and secrete proinflammatory cytokines, chemokines, and growth factors, resulting in eosinophilic inflammation [12]. The blood eosinophil count has been proposed as a biomarker for directed therapy in COPD [13, 14]. Eosinophil counts >2% have been associated with better response to both oral [13] and inhaled corticosteroids (ICS) [15, 16]. Targeted ICS therapy in COPD has previously been proposed, considering the risk-benefit ratio of corticosteroid therapy [14]. Non-AATD COPD and AATD-associated COPD share disease modifiers, including genetic (e.g., *IREB2* polymorphism) [17, 18] and environmental factors (e.g., cigarette smoke and air pollution [19, 20]). Blood eosinophilia might also be a marker of a disease-modifying factor common to non-AATD COPD and AATD; hence we hypothesized that AATD patients who are defined as eosinophilic will have a better response to ICS therapy – and therefore better outcomes when on such treatment – compared to those not eosinophilic.

The aim of this study was therefore to compare the patients' clinical phenotype and outcomes according to blood eosinophil status. We also aimed to examine whether ICS use affects these outcomes differently according to eosinophil count.

Subjects and Methods

Subjects

The UK AATD registry (ADAPT) was established more than 20 years ago and is described in detail elsewhere [21]. Briefly, it is a single-center study where patients undergo annual lung physiology testing, biological sample collection (including a full blood count), and clinical assessment. Lung functional decline has been determined in all patients with ≥ 3 years of follow-up, excluding patients transplanted during this period and those who had received α_1 -antitrypsin augmentation or other potential disease-modifying therapy in clinical trials. The methods for calculation of decline have previously been described [22].

The ADAPT project has overarching ethics approval from the South Birmingham LREC (3359 and 3359a), and patients give informed consent at baseline for data collection and storage.

Study Design

All patients with PiSZ and PiZZ genotypes, with at least one blood eosinophil count, were selected. Blood "eosinophilia" was defined as a count $>0.2 \times 10^9/L$, on the basis that this value picked up 91% of the patients whose count was $>2\%$, and 2% appears to be therapeutically important [13]. This cutoff was chosen for the purpose of specificity in line with previous work by contemporaries in the field [13, 14, 23]. We further classified eosinophilia into 3 groups (always, intermittent, or never present) based on the frequency this occurred in serial blood counts examined for a period up to 10 years from the initial (baseline) visit to our center.

As part of a national database of AATD, serial blood tests were taken for research purposes only. Routine clinical blood tests for patients from the region were not incorporated into the database. The blood tests were taken in stable state only. In case of exacerbation, follow-up was deferred until at least 6 weeks after the resolution of the exacerbation. The authors used both symptom-based and healthcare definitions to identify exacerbations through structured self-reporting questionnaires and from review of the medical notes. Exacerbations were classified according to Anthonisen types (1, 2, or 3). Survival amongst ADAPT patients on the registry was checked with medical practitioners and patient families and on death certifications.

We also determined which patients had a clinical picture indicative of asthma-COPD overlap syndrome (ACOS) [24] using their medical records (see online suppl. Methods and Results; see www.karger.com/doi/10.1159/000481867 for all online suppl. material). Medical records were also used to assess the average exacerbation frequency and to determine which classes of medication the patients took.

Methods

All analyses were carried out in SPSS (SPSS® version 20; IBM, Armonk, NY, USA). Univariate analyses compared eosinophilic and non-eosinophilic patients for demographics, bronchodilator reversibility (BDR), clinical phenotype (including ACOS, asthmatics who smoke, and exacerbations), lung function, CT densitometry (where available), survival, and lung functional decline. FEV₁ decline was calculated via regression analysis using at least 4 lung function measurements taken over a minimum period of 3 years, as described previously by both Pillai et al. [21] and Wood et al. [22]. No interactions were sought between eosinophil count and time with respect to FEV₁ decline.

Table 1. Characteristics at baseline

	Whole group (<i>n</i> = 760)	PiZZ group (<i>n</i> = 710)	PiSZ group (<i>n</i> = 50)
Age, years	51.25 (16.95)	51.3 (16.04)	50.73 (27.49)
Male	443 (58.29%)	416 (58.59%)	27 (54%)
Smoking status			
Current	25 (3.29%)	15 (2.11%)	10 (20%)
Ex	410 (53.95%)	392 (55.21%)	18 (36%)
Never	135 (17.76%)	116 (16.34%)	19 (38%)
Not available	190 (25%)	187 (26.33%)	3 (6%)
Pack-years	12.5 (23.00)	12.63 (23.00)	11.00 (30.00)
ICS	16.5 (21.00)	16.5 (21.00)	–
No ICS	12 (23.00)	12.00 (23.00)	13.00 (35.00)
FEV ₁ , % predicted	52.43 (47.84)	51.67 (45.72)	89.8 (44.5)
FVC, % predicted	103.1 (35.91)	103.1 (35.98)	103.36 (34)
TLC, % predicted	112.95 (21.67)	113.73 (21.02)	98.5 (22.5)
RV, % predicted	114 (49.42)	115.11 (49.34)	97 (27.5)
BDR	206 (27.11%)	191 (26.9%)	15 (30%)
Number of eosinophil counts	4 (4)	4 (4)	2 (2)
Eosinophils >0.2 × 10 ⁹ /L	124 (16.32%)	115 (16.2%)	9 (18%)
ACOS	16 (2.1%)	13	3
Treatment at baseline ^a			
LAMA	303 (39.87%)	296 (41.69%)	7 (14%)
LABA/ICS	323 (42.50%)	317 (44.65%)	6 (12%)
ICS ^b	211 (27.76%)	210 (29.58%)	1 (2%)
Xanthines	55 (7.24%)	54 (7.61%)	1 (2%)
Exacerbations/year	0.4 (1.1)	0.43 (1.2)	0.00 (0.33)

The table shows clinical features at the first assessment for our registry. Values are shown as mean (standard deviation) or median (interquartile range), dependent on their distribution, or *n* (%). ICS, inhaled corticosteroids; BDR, bronchodilator reversibility; ACOS, asthma-COPD overlap syndrome; LAMA, long-acting muscarinic antagonist; LABA, long-acting β -adrenoceptor agonist. ^a Typical classes of treatment for COPD and/or asthma only are shown. ^b Where taken separately from LABA, or without LABA. Note that no patients received augmentation therapy, as this is not available in the UK.

Analysis

Analyses were performed using χ^2 tests for categorical variables and Mann-Whitney U tests for continuous variables, substratifying by Pi phenotype. Covariables for logistic, linear, and Cox regression analyses were selected if $p < 0.15$ in univariate analysis and if there was no significant collinearity with another included variable. Prior literature on influences on mortality [25] and decline [22, 26, 27] in AATD was used to aid in the prioritization of covariables where necessary. Age, baseline FEV₁, BDR, exacerbations, and smoke exposure were used as covariates in the regression analysis. Smoke exposure was defined as “current,” “ex,” or “never.” The analyses of longitudinal outcomes were further substratified by ICS use, in order to compare whether eosinophilic and non-eosinophilic patients differed according to the treatment they received. We did not exclude patients from multivariate analysis if data on a covariable were missing. All results from the multivariate analysis are reported as two-tailed; significance was taken at $p < 0.05$.

Results

Cross-Sectional Analyses of Clinical Phenotype

The cohort consisted of 760 PiZZ and 50 PiSZ patients enrolled between November 1996 and December 2014; their demographic characteristics are shown in Tables 1 and 2. Smoking history and pack-year smoke exposure data were available for 570 participants (75%). No patients were found to be taking oral corticosteroids at the time of follow-up. This may be because the patients were not seen during or within 6 weeks of an exacerbation. In our group, 16.32% of the patients had an eosinophil count >0.2 × 10⁹/L at baseline and were classified as being eosinophilic.

In those participants with eosinophilia at baseline (eosinophil count >0.2 × 10⁹/L) the average eosinophil count at baseline was 0.39 × 10⁹/L (0.012), compared to 0.11 ×

Table 2. Characteristics of the patients stratified by the pattern of blood eosinophils over time

	Always (<i>n</i> = 48)	Intermittent (<i>n</i> = 348)	Never (<i>n</i> = 250)	<i>p</i> value
Age, years	49.42 (13.06)	51.16 (16.21)	51.88 (19.64)	0.760
Male	33 (68.75%)	213 (61.21%)	131 (52.4%)	0.031
Smoking status				0.245
Current	0	9 (2.58%)	9 (3.6%)	
Ex	31 (64.58%)	200 (57.47%)	123 (49.2%)	
Never	5 (10.42%)	70 (20.11%)	46 (18.4%)	
ACOS (<i>n</i> = 16)	4 (25%)	2 (12.5%)	10 (62.5%)	0.000
FEV ₁ , % predicted	50.53 (35.57)	52.51 (43.44)	59.36 (53.56)	0.005
FVC, % predicted	103.20 (39.08)	106.38 (32.33)	104.68 (33.5)	0.809
TLC, % predicted	110.12 (21.92)	112.74 (21.65)	112.14 (22.26)	0.488
RV, % predicted	116.56 (61.83)	114.76 (45.16)	110.26 (50.91)	0.248
BDR	15 (31.25%)	110 (31.61%)	63 (25.2%)	0.222
Exacerbations/year	0.25 (1.54)	0.43 (1.00)	0.25 (1.00)	0.007
Number of eosinophil counts	2.5 (2)	5 (4)	3 (3)	0.000
Death during follow-up	9 (18.75%)	42 (12.07%)	25 (10%)	0.217

The table shows the clinical features of those patients with repeated eosinophil counts available. 114 patients had only a baseline count; hence no persistence rating over serial samples could be allocated. Values are shown as mean (standard deviation) or median (interquartile range), dependent on their distribution, or *n* (%). BDR, bronchodilator reversibility; ACOS, asthma-COPD overlap syndrome.

Fig. 1. Prevalence of blood eosinophil counts $>0.2 \times 10^9/\text{L}$ in 3 groups of α_1 -antitrypsin deficiency patients based on the frequency this occurred in serial blood counts. The bar chart shows the proportion of patients whose blood eosinophil counts exceeded $0.2 \times 10^9/\text{L}$ on more than one occasion. 114 patients had only one count; hence they were excluded from this analysis.

$10^9/\text{L}$ (<0.01) in those who had a count ≤ 0.2 . During follow-up, which ranged from 1 to 18 years, 53.9% of the patients exhibited an eosinophil count $>0.2 \times 10^9/\text{L}$ on at least one occasion (intermittent), 7.4% always exhibited a

value in this range (always), and 38.6% did not demonstrate an eosinophil count $>0.2 \times 10^9/\text{L}$ on any occasion (never) (shown in Fig. 1 and Table 2). Patients defined as eosinophilic throughout follow-up were more likely to be male (68.75%) and they had a lower baseline FEV₁ (50.53% predicted, compared to 59.36% predicted in the never-eosinophilic group) as shown in Table 2. Eosinophil count, when used as a scale, was not associated with exacerbation rate ($p = 0.2$), but there was a small difference in exacerbation rate between the 3 groups (always, intermittent, and never; Table 2). As it was highest in the “intermittent” group and lower in both the “always” and the “never” group, this could be a chance finding. Seventy-six participants died during follow-up (Table 2); survival status was available for all patients within the database.

Patients with ACOS are defined in part by eosinophil count and BDR [24]. In all, 2.1% of the patient cohort fulfilled this definition. However, the number was very small (16 patients), so that a comparison of ACOS patients with non-ACOS patients was likely underpowered and generally uninformative; hence all further results pertaining to ACOS are shown in the online supplementary material.

Longitudinal Outcomes

FEV₁ decline and mortality rate stratified for eosinophil status are shown in Figure 2 and Table 2. A significant difference in FEV₁ decline between eosinophilic

Fig. 2. FEV₁ decline according to blood eosinophil count grouping (based on the frequency this occurred in serial blood counts) and inhaled corticosteroid (ICS) use. The bar chart shows the mean decline in mL/year. There were no significant differences in decline in the univariate analyses ($p = 0.332$), but in the multivariate analysis the difference between those never and those always eosinophilic was notable, as described in the text.

groups was not detected in univariate analyses ($p = 0.332$). Multivariate analyses assessing FEV₁ decline and survival were conducted on the PiZZ patients only, since the PiSZ cohort was small, hence insufficient covariates could be included. The analyses, adjusted for age, baseline FEV₁, BDR, exacerbations, and smoke exposure, showed that blood eosinophil count is associated inversely with decline ($p = 0.037$), such that those always eosinophilic exhibited a decline 9.2 mL/year less than those never eosinophilic. If the baseline count alone was used, this relationship was absent. The odds ratio for decline more rapid than with normal ageing (i.e., decrease $\geq 1\%$ predicted per annum) was 2.5 (95% CI 1.5–4.4) in patients who were never eosinophilic compared to those always eosinophilic ($p = 0.001$).

The Cox regression analyses did not show any difference in survival ($p > 0.05$) between the eosinophilic and non-eosinophilic patients, whether using the always/intermittent/never grouping or just the baseline value.

ICS Treatment

Most patients were taking ICS at baseline (Table 1). These individuals were more likely to have eosinophils $>0.2 \times 10^9/L$ ($p = 0.002$) and had lower FEV₁ and DLCO (both $p < 0.001$) and a greater pack-year smoke exposure (16.5 vs. 7.8 pack-years, $p < 0.001$). FEV₁ decline did not differ between the eosinophil groups or by ICS use in the univariate analyses. However, when the multivariate analyses for FEV₁ decline were stratified for baseline ICS

use, the relationship of persistent eosinophilia to slower decline persisted in those on ICS, but not in the remainder. Exacerbation frequency was not independently associated with eosinophil count in those taking ICS ($p = 0.34$), and in those not on ICS the small difference in rate between the eosinophil groups seen in the univariate analyses (always group, 0.25 exacerbations/year; intermittent group, 0.43; never group, 0.25; $p = 0.048$) was lost after adjustment for covariates ($p > 0.5$).

Discussion

We have shown that blood eosinophil count is a clinically relevant biomarker in this cohort of AATD patients. The results indicate that blood eosinophil count may have the potential to aid in the personalization of therapy for these patients in a similar manner to non-AATD COPD patients. The similarity between the prevalence of blood eosinophilia in AATD and the prevalence in both healthy individuals [28] and non-AATD COPD patients [7–11] suggests that it could mark a pathogenic feature common to all groups, independent of AATD. The similar impact of eosinophilia on PiSZ and PiZZ patients also implies that the overall phenotype a patient with COPD exhibits is a composite of many risk factors, with AATD being one.

A cutoff of 2% blood eosinophils has previously been found to be related to response to oral and inhaled steroids, but an absolute count that defines this is less clear. In our cohort, 100% of the patients with blood eosinophils $>0.3 \times 10^9/L$ and 91% of the patients with blood eosinophils $>0.2 \times 10^9/L$ reached the 2% threshold. We therefore chose eosinophils $>0.2 \times 10^9/L$ to determine eosinophilic status, in order to ensure greater sensitivity without significantly compromising specificity. We felt sensitivity to be the more important factor, since we would not wish to miss cases with an aspect of airway disease that has a potentially different treatment algorithm. This threshold is similar to that found equivalent to 2% in the ECLIPSE study [28]. Our results, however, indicated that a single eosinophil count would be insufficient to direct eosinophilic therapy (such as ICS) as baseline count alone was not associated with lung functional decline, whereas a persistently high ($>0.2 \times 10^9/L$) count was. This important finding was not apparent in the univariate analyses; this may be because both ICS and FEV₁ decline are related to baseline FEV₁. Hence the most valid comparison is the multivariate analysis, which took this and other factors that may influence decline into

account. In this analysis, non-eosinophilic patients were more likely to exhibit a decline faster than with normal ageing. The concept of assessing decline as deterioration in percent predicted, rather than in mL/year, was proposed in 2013 [29] and used recently in our cohort. We demonstrated that a significant proportion of patients exhibit stable disease when assessed in this way, and we discussed the value of this method and its impact on therapy choices [30].

A number of clinical subgroups in non-AATD COPD and asthma have shown an association with peripheral blood eosinophilia [3]. ACOS, asthmatics who smoke, COPD exacerbations, and positive bronchodilator response have all been related to increased eosinophilic inflammation [3]. However, in our cohort, using multivariate analyses there was no significant difference in BDR (although a trend toward a relationship was seen), pack-years, smoking status, or exacerbation rate between the patients exhibiting persistent eosinophilia and those with absent eosinophilia. In our cohort, those who were always eosinophilic were more likely to be male. Those with persistent eosinophilia, however, did have a lower percent predicted FEV₁ at baseline (50.53%) than those in the never-eosinophilic group (59.36%). In the ECLIPSE study, the authors found that those in the eosinophilic group were more likely to be male, but had milder disease symptoms and a lung functional decline comparable to those who were not eosinophilic. In our cohort, the reasons for the male predominance and lower FEV₁ among the eosinophilic patients were unclear, and in some respect the results were counterintuitive, given that their symptoms were milder and their decline was similar to that of non-eosinophilic patients. Neither baseline eosinophil count nor serial counts $>0.2 \times 10^9/L$ exhibited many clinical associations, as such patients would be difficult to identify unless blood counts were examined repeatedly.

The pathology marked by blood eosinophilia may be eosinophilic pulmonary inflammation. Blood eosinophilia has been shown by several studies to be reflective of sputum eosinophilia, albeit weakly correlated [28], perhaps because of the inherent variability in sputum samples. We have previously shown that serial sputum samples can be used to reduce variability in AATD sputum analyses [31], which may prove more useful. A small number of patients had several sputum cytospins available, but the heterogeneity in clinical features between these patients meant that interpreting data in relation to their blood count would be inappropriate. Consequently, we were unable to assess whether airway eosinophilia was directly related to blood eosinophilia in our cohort.

In longitudinal analyses, eosinophilic patients appeared to have a better prognosis as they generally had a slower decline in lung function. This was demonstrated by the fact that non-eosinophilic patients were more than twice as likely to deteriorate faster than with normal ageing (odds ratio 2.5; $p < 0.0001$) as their eosinophilic counterparts. We chose to use this definition, rather than only describing decline in mL/year of FEV₁ lost, as it is more physiological, thus was deemed important for AATD by European experts [29], and appeared to better identify the stable patients in our group [30]. A better prognosis has previously been reported for eosinophilic patients in the ECLIPSE and CHAIN cohorts of non-AATD COPD patients, using outcomes of emphysema progression and mortality, respectively [28, 32]. This feature was only seen in our cohort if the patients had received ICS, suggesting that their ability to react to this treatment could have been responsible for the favorable prognosis. This is consistent with post hoc analysis of various ICS/long-acting β -adrenoceptor agonist studies in COPD, including the FORWARD study, where patients exhibiting the highest eosinophil counts also exhibited the greatest reduction in exacerbations and improvement in quality of life if receiving ICS, and studies of fluticasone furoate/vilanterol, where exacerbation reduction was again a major feature for the more eosinophilic participants [15, 16]. We did not show a difference in exacerbation rate between eosinophilic and non-eosinophilic patients; however, the exacerbation rates were generally low, which likely compromised the power to detect any effect.

Oral and inhaled corticosteroids are widely used in clinical practice for exacerbating and stable COPD, respectively. In a small study of 5 PiZZ patients, Wilcke and Dirksen [33] have previously identified the potential benefit of ICS in improving lung function in patients with AATD-related emphysema. However, corticosteroid therapy carries a significant side effect burden, including oral thrush, adrenal suppression [34], and pneumonia [35, 36]; hence indiscriminate use could cause harm without therapeutic benefit. Studies have previously shown that blood eosinophil count can be reliably used to direct oral corticosteroid therapy in exacerbations [13] and imply that reduced exacerbation rates are the key benefit for eosinophilic patients [15, 16]. Our data go one step further and demonstrate a link to FEV₁ decline. Whilst, historically, FEV₁ and exacerbations have been the main drivers to ICS use in stable COPD, our data may imply that blood eosinophil count and FEV₁ decline could also be used to aid in the selection of patients. Rational use might include receipt of ICS if blood eosinophils are

$>0.2 \times 10^9/L$ and either exacerbations or excessive FEV₁ decline are occurring. ACOS patients might also be an important therapeutic group, partially defined by blood eosinophil count, but the small number of patients in our cohort with this syndrome meant that we did not find it a useful phenotype in our analyses. In order to verify its potential for biomarker-directed therapy, a large prospective study is needed to evaluate whether blood eosinophil count is a robust determinant of response to ICS therapy in COPD.

Our study is strengthened by the availability and breadth of patient data available for this relatively rare disease, in particular the availability of repeated blood analyses and long-term follow-up. There are, however, some weaknesses which should be considered when interpreting the results of this study. Notably this post hoc analysis of an AATD cohort was not designed specifically to assess eosinophilic inflammation. Although the results support similar findings from studies on non-AATD COPD, they specifically pertain to the AATD population. Furthermore, due to the retrospective nature of this analysis there were specific areas where data were not available for analysis. This is in part due to the long-standing nature of the national AATD database, which has evolved alongside the ADAPT project for over 20 years. In addition to this, although repeated blood tests were available for blood eosinophils, the number of serial blood tests available was limited. Those in the “intermittent” group had, on average, more blood tests than those in the “always” and “never” groups, which may have had a confounding effect on the classification of eosinophilic status. Those with more blood tests available have a higher chance of being assigned to the intermittent group. Furthermore, those patients who experience more exacerbations may attend follow-up comparatively less often than those who have fewer exacerbations; thus such frequent

exacerbators may be underrepresented in this cohort. Nevertheless, our findings suggest that patients with AATD who demonstrate persistent blood eosinophilia over time demonstrate a slower decline in lung function when on ICS therapy than those who never demonstrate blood eosinophilia. This difference disappears when not using ICS, implying a new direction for informing the choice of corticosteroid therapy for stable AATD patients.

Conclusion

Blood eosinophil levels persistently $>0.2 \times 10^9/L$ may be an indication for ICS use in PiZZ AATD in order to reduce FEV₁ decline. Prospective studies would be needed to validate this hypothesis.

Financial Disclosure and Conflicts of Interest

In the past, the ADAPT study received funding in the form of a noncommercial grant from Grifols. A.M.T. currently receives noncommercial funding from Grifols and the Alpha-1 Foundation, and R.A.S. from CSL Behring.

Author Contributions

E.V.L. is the first author; she was involved in data collection, assimilation, and statistical analysis and co-wrote the manuscript. S.M.H. reviewed the data and completed the statistical analysis. S.Z. collected data pertaining to eosinophil counts and lung function from the ADAPT database. D.K. collected data pertaining to sputum eosinophils and reviewed the manuscript. R.A.S. reviewed the manuscript. A.M.T. acts as the guarantor assuming overall responsibility for the research; she formulated the research question, supervised data collection and the statistical analysis, and led the manuscript preparation.

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