α_1-Antitrypsin deficiency and chronic respiratory disorders

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AATD is a hereditary disorder associated with a high risk for the development of several lung diseases. There is a need to answer different questions about epidemiology, genetics, pathophysiology, clinical management and prognosis of these lung diseases. http://bit.ly/2IHQGOp

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ABSTRACT α_1-antitrypsin deficiency (AATD) is a hereditary disorder associated with a risk of developing liver disease and pulmonary emphysema, and other chronic respiratory disorders (mainly asthma and bronchiectasis); Z variant is the commonest deficient variant of AAT. Determining AAT concentration in serum or plasma and identifying allelic variants by phenotyping or genotyping are fundamental in the diagnosis of AATD. Initial evaluation and annual follow-up measurement of lung function, including post-bronchodilator forced expiratory volume in 1 s and gas transfer inform on disease progression. Lung densitometry is the most sensitive measure of emphysema progression, but must not be use in the follow-up of patients in routine clinical practice. The exogenous administration of purified human serum-derived AAT is the only approved specific treatment for AATD in PiZZ. AAT augmentation therapy is not recommended in PiSZ, PiMZ or current smokers of any protein phenotype, or in patients with hepatic disease. Lung volume reduction and endoscopic bronchial valve placement are useful in selected patients, whereas the survival benefit of lung transplant is unclear. There are several new lines of research in AATD to improve the diagnosis and evaluation of the response to therapy and to develop genetic and regenerative therapies and other treatments.

Introduction

α_1-antitrypsin deficiency (AATD) is an underrecognised genetic disorder [1]. It is not a disease in itself, but rather a predisposition for the development of a number of diseases, mainly pulmonary emphysema and other chronic respiratory disorders with different clinical manifestations and frequent overlap, and several types of hepatopathies in both children and adults.

AAT is the most prevalent proteases inhibitor in the human serum [1]. It is primarily produced in high quantities and secreted mainly by hepatocytes [2]. AAT is an important anti-protease in the lung, but it also has significant anti-inflammatory effects on several cell types and modulates inflammation caused by host and microbial factors. In effect, it can play an important role in modulating key immune cell activities and protecting the lungs against damage caused by proteases and inflammation.

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The genetics of AATD

AAT is coded by the serine-protease inhibitor (*SERPINA1*) gene which encodes a 52 kDa AAT protein whose locus is located on chromosome 14q32.1 close to immunoglobulin heavy chain cluster [3]. Mature AAT protein is secreted in the blood after cleaving the first 24 amino acids of the N-terminal region which codes for signal peptide in the rough endoplasmic reticulum. However, AAT is a polymorphic protein with >100 genetic variants coded for by two alleles in a co-dominant manner [4]. Many of these reflect point mutations in the gene sequence leading to amino acid substitutions, which may affect the electrophoretic mobility of the resulting AAT protein.

In effect, a large body of evidence has shown that *SERPINA1* is highly polymorphic, and mutations in this gene cause a hereditary co-dominant autosomal disorder [5]. Pathological *SERPINA1* variants are classified as either deficient or null. Deficient variants occur as a result of a point mutation that causes retention of the AAT in the cytoplasma. Null mutations generally occur owing to the presence of a premature stop codon and patients with these mutations have no detectable AAT in serum.

Isoelectric focusing detects these variants, which are labelled A–Z depending on their mobility, *i.e.* faster or slower, compared to the most common (normal variant) labelled M, branded with earlier or later letters, respectively [4]. Other common variants are S and Z, with MM, MS, MZ, SS, SZ and ZZ protein phenotypes accounting for >99% of all variants in most of population surveys. Dysfunctional variants lead to abnormal function of AAT, with reduced binding to neutrophil elastase (as in the F variant) or, as with Pittsburgh, structural abnormality that causes the protein to serve as a thrombin inhibitor rather than as an anti-elastolytic protein, causing a bleeding diathesis [6].

Common M alleles account for ∼95% of those observed in the Caucasian population, and are characterised by normal levels of serum AAT [3], with serum AAT levels ranging between 102 and 254 $mg{\cdot}dL^{-1}$ [7]. AAT alleles that confer high risk for the pathogenesis of pulmonary emphysema are those in which deficiency or null alleles are combined in homozygous, heterozygous or compound heterozygous states that result in serum AAT levels below a defensive threshold (57 $mg{\cdot}dL^{-1}$) [7]. The MS variant of AAT is associated with minor reductions in serum AAT levels (86–218 $mg{\cdot}dL^{-1}$) [7].

Z variant of AAT, characterised by one amino acid substitution of lysine for glutamic acid at position 342 is the commonest deficient variant [6]. It has reduced capacity to inhibit neutrophil elastase. Serum AAT levels in subjects with the MZ phenotype are 62–151 $mg{\cdot}dL^{-1}$ [7]. Presence of two copies of mutant Z allele is associated with severe AATD with serum levels ranging between $\leqslant$29 and 52 $mg{\cdot}dL^{-1}$ [7].

Controversial results have been published revealing chronic obstructive pulmonary disease (COPD) risk among protease inhibitor (Pi)MZ heterozygotes. A normal protease/antiprotease balance exists in healthy (MM) individuals, in which high levels of MAAT surround the resting neutrophil [8]. During exposure to increasing levels of interleukin (IL)-8 the cell moves down a concentration gradient of AAT and up a gradient of IL-8, thus leading to neutrophil migration to the area of inflammation [2]. Nonsmoking MZ individuals have intermediate levels of AAT and increased sputum IL-8 levels and neutrophil counts. In AATD individuals homozygous for the Z allele, low levels of circulating ZAAT surround the neutrophil and the described AAT gradient is grossly disrupted, resulting in increased chemotactic responsiveness of neutrophils with an overwhelmed anti-protease defence that contributes to the development of COPD. In smoking MZ individuals, reactive oxygen species in cigarette smoke inactivate AAT, resulting in a protease/antiprotease imbalance with increased amounts of neutrophil elastase. Polymerisation of ZAAT protein and increased amounts of IL-8 intensify neutrophil influx into the MZ lung, which could facilitate the development of COPD [2, 8]. In fact, ZAAT polymers found within lungs can also fuel inflammation in the AAT deficiency [3]. Since ZAAT polymers are chemotactic for neutrophils, co-localisation can trigger the release of myeloperoxidase and upregulation of neutrophil adhesion molecules [3]. It has been found that ZAAT polymers co-localise with neutrophils in the alveoli of patients with AAT deficiency [3].

Accumulation of ZAAT in the rough endoplasmic reticulum of hepatocytes leads to reduced availability of AAT in the circulation, and thus AAT is insufficient to neutralise the excessive amount of protease synthesised, especially in the lungs during the course of inflammation [3]. Presence of Z-polymer in the circulation and in bronchoalveolar lavage fluid of patients with severe AATD generates a substantial concentration dependent influx of neutrophils that is not driven by chemokines. Furthermore, ZAAT creates endoplasmic reticulum stress in the hepatocytes, which may have severe consequences in the liver ranging from liver cirrhosis to hepatocellular carcinoma directly [3].

The rarer null variants that include a variety of gene insertions, deletions and point mutations can result in the absence of AAT production, and null heterozygotes can appear to be normal (M_{null}) or abnormal (Z_{null}) based on the electrophoretic pattern of protein phenotyping, although not consistent with expected

family inheritance. Other deficient mutations such as M_{Malton}, $M_{Wurzburg}$ and $M_{Heerlen}$ also display an M-protein electrophoretic phenotype.

Data provided by 224 cohorts selected from the 65 countries have enabled the estimation of the presence of a total of 253 404 ZZ genotypes worldwide, distributed as follows: Europe (n=119 594), America (n=91 490), Africa (n=3824), Asia (n=32 154), and Australia (n=4126) and New Zealand (n=2216) [9].

Looking at the distribution of PiZZ prevalence in Europe, it is possible to note that the highest prevalence is in the south of the Scandinavian peninsula, Latvia and Denmark, and it progressively decreases towards the south and the east of Europe, whereas the highest prevalence of PiSZ is in the Iberian peninsula and southern France and gradually decreases towards the north, south and east of the continent [1]. In effect, ~2000 years ago, the Z mutation arose and persisted in the Swedish population [10]. With the travels of the Vikings, the Z gene was gradually disseminated throughout the Baltic region and thereafter more widely by sea and land travel, and its prevalence followed this, such that there is a gradient of 1 in 1600 in Denmark to 1 in 5000 in the United States. The survival benefit of the heterozygous state has never been explained satisfactorily, although the homozygous state has been suggested to increase fertility [10].

Diseases associated with AATD

As already mentioned, AATD predisposes mainly to liver disease and pulmonary emphysema, but patients with AATD might also be affected by other chronic respiratory disorders, granulomatosis with polyangiitis, and panniculitis [5].

Pulmonary emphysema and COPD

Pulmonary emphysema has an earlier onset than in patients with COPD and often appears to be out of proportion to patients' smoking history [11]. Lung function tests on symptomatic patients often show evidence of increased lung volumes and air trapping as well as impaired gas transfer. Nevertheless, even patients with severe airways obstruction and prominent emphysema on computed tomography (CT) scan may have normal gas transfer.

Patients with AATD may present with a severe airflow limitation that is often disproportionate to their smoking history, and without any airways obstruction [11]. Furthermore, they do not always present airflow obstruction and parenchymal destruction concurrently. Often airflow limitation is not fixed and, consequently, there is a wide variation in bronchodilator response in these patients. The degree of lung function impairment can vary greatly among patients with the same phenotype for AATD, and can be significantly different in siblings with the same phenotype. The risk factors that are able to affect the rate of change in lung function in AATD are similar to those identified for COPD (smoking, exacerbations, environmental exposures, bronchodilator reversibility, age and basal lung function) [11].

The symptoms and signs in AATD can be similar to features of asthma. >40% of patients have chronic sputum expectoration, even if they are nonsmokers [11]. Patients with chronic bronchitis are inclined to suffer from more severe airflow obstruction and widespread emphysema than those without, notwithstanding similarities in age and smoking history [11].

It has been reported that exacerbations occurred in ~50% of patients who attended the UK registry and the mean duration of episodes was ~15 days [11]. The exacerbation episodes are associated with a greater degree of inflammation than in patients not deficient in AAT [12].

The risk of emphysema and COPD in heterozygotes

There is substantial difference in pulmonary phenotype and prognosis between PiSZ patients and those who are PiMM and PiZZ [13]. PiSZ subjects are less susceptible to cigarette smoke than PiZZ individuals. It has been observed that the proportion of emphysema and COPD cases occurring at <20 pack-years was greater in PiZZ patients. Differences in emphysema between PiSZ and PiZZ patients were more marked in the lower zones; 42.9% of PiSZ patients scanned had upper-zone-dominant emphysema compared with 14.1% of PiZZ patients. Median decline was greatest when baseline FEV_1 was 50–80% predicted (PiZZ -56.3 mL·year^{-1}, PiSZ -65.3 mL·year^{-1}) and there was no difference in annual decline of FEV_1 or gas transfer (diffusing capacity of the lung for carbon monoxide (D_{LCO}) and carbon monoxide transfer coefficient % pred) when analysed as categories or continuous variables (smoking status, presence of COPD and index status, adjusting for baseline lung function and age). PiSZ patients had better survival than PiZZ.

Many PiSZ patients look phenotypically similar to usual COPD at their first assessment. Logistic regressions, adjusting for age, smoke exposure and baseline FEV_1 demonstrated that PiSZ patients had a similar risk of emphysema and bronchiectasis, but lower risk of chronic bronchitis when compared with PiMM patients [13].

Never-smoking PiMZ subjects do not have an increased risk of COPD [4]. Smoking PiMZ subjects have an increased risk of COPD compared to smoking PiMM subjects.

The role of other heterozygotes remains unknown due to their rarity and potential ascertainment bias from measuring AAT in unusual cases of lung or liver disease [4].

Asthma

Lung disease in AATD generally presents at a younger age than "usual" COPD and may be misdiagnosed as asthma [4]. However, AATD can coincide with asthma, and patients with both AATD and asthma are more susceptible to developing an accelerated and progressive loss of lung function because of constant unchecked inflammation [14]. Although the aetiology and disease mechanisms of asthma and AATD are distinct, patients with AATD commonly first present with asthma-like symptoms [15]. Adding to the confusion, it has been recognised that allergy and asthma often coexist with AATD [15].

AATD itself might predispose to airway hyperresponsiveness, an essential ingredient for reversible airflow obstruction, and participate in asthma pathophysiology [15]. The underlying biological mechanism is not understood. Airway inflammation and remodelling in asthma involves degradation of the extracellular matrix, most prominently elastin, and is characterised by an imbalance between elastase and its primary inhibitor AAT [16]. It has long been documented that neutrophil elastase is significantly increased in the induced sputum from asthma patients compared with control subjects, and neutrophil elastase levels in asthmatic patients are correlated with a decline in FEV_1 [17], and computationally intensive analysis of induced sputum proteome has allowed to documented that *SERPINA1* is significantly upregulated in asthma [18]. Recently, it has also been shown that elastase promotes an inflammatory phenotype and increased sensitivity to acetylcholine in airway smooth muscle tissues by disrupting signalling pathways mediated by integrin-associated adhesion complexes [19]. Obviously, the presence of AATD can amplify the effect of elastase. In any case, data from basic research have suggested that AAT has immunomodulatory functions and might affect eosinophils [20].

A recent study conducted through the Alpha-1 Foundation Research Registry, involving 500 patients with severe AATD, has provided evidence that nearly 46% of all participants were diagnosed with either asthma or allergic disease [21]. However, among the 34% participants undergoing allergological evaluation, only 5% were diagnosed with AATD by their allergist. This finding suggests that if a patient enters the healthcare system through allergists, this often delays the appropriate diagnosis and treatment.

A Spanish study that explored the AAT distribution in an allergic asthmatic population reported that 22.4% of asthmatic patients had at least one mutated allele (S or Z) [22]. However, no association between the different genotypes and asthma severity was found and no significant differences in all clinical and functional tests, as well as nasal eosinophils, IgA and IgE serum levels were observed. Peripheral eosinophils were significantly lower in patients with the PiMS genotype. Neither association between deficient AAT genotypes or serum AATD and development of severe asthma, nor correlation between ATT levels and FEV_1 were observed. These findings confirmed what reported years before by VAN VEEN *et al.* [23] who highlighted that AAT heterozygoty does not seem to be an important risk factor of persistent airflow limitation in patients with asthma. Therefore, routine assessment of the AAT phenotype is not indicated in asthmatic patients even if they exhibit fixed airflow limitation [23].

Nevertheless, although fixed or nonreversible obstruction in patients with asthmatic symptoms in most cases is secondary to remodelling, in some cases it may result from AATD and the presence of symptoms, onset in the fourth decade, nonreversible airways obstruction and panlobular (panacinar) emphysema should raise suspicion and promote further investigations to check for AATD [24].

Bronchiectasis

Bronchiectasis has also been associated with AATD, with the mechanistic link of incompletely opposed neutrophil elastase activity [25]. There is concrete evidence of a direct impact of neutrophil elastase on bronchiectasis disease progression through effects on ciliated epithelium, mucus production, emphysema development and inactivation of the immune response [26]. However, whether bronchiectasis comes from a primary mechanism of the disease or is the result of recurrent respiratory infection is still matter of debate [27].

Several reports have suggested an association between AATD and bronchiectasis. A study that involved subjects with severe AAT deficiency (PiZZ phenotype) reported an unexpectedly high prevalence of bronchiectatic changes in almost all patients (94.6%) without regard to clinical manifestations [25]. If criteria for clinically significant bronchiectasis were applied, *i.e.* chronic cough with sputum production in association with bronchial dilation in at least four bronchial segments, bronchiectasis occurred in 27% of the study population. An analysis of seven cohorts of adult outpatients with bronchiectasis prospectively

enrolled in different countries across Europe identified AATD as a cause of bronchiectasis in 0.6% of the population [28]. However, a large targeted screening programme for AATD in Germany showed that 9.82% of the tested population at the AAT laboratory at the University of Marburg were suffering from severe AATD and bronchiectasis, along with emphysema and COPD, demonstrated to be a strong predictor for the PiZZ genotype, suggesting the implementation of screening in this emerging population [29]. A recent analysis of the US Bronchiectasis Research Registry reported that bronchiectasis was associated with a physician diagnosis of severe AATD in 9.4% of 615 participants included in the evaluation [30]. A greater percentage presented mycobacterial lung involvement.

Best practice in diagnosis of pulmonary diseases in AATD

There are some minor differences in the recommendations of the US Alpha-1 Foundation [31] and European Respiratory Society [4] for the best practice in diagnosis of pulmonary diseases in AATD (table 1).

TABLE 1 The best practice in diagnosis of pulmonary diseases in α_1-antitrypsin deficiency (AATD) according to the recommendations of the US Alpha-1 Foundation [31] and the European Respiratory Society (ERS) [4]

	US Alpha-1 Foundation	ERS
Laboratory testing for AATD		
	All individuals with COPD regardless of age or ethnicity; all individuals with unexplained chronic liver disease; all individuals with necrotising panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis should be tested for AATD Parents, siblings and children, as well as extended family of individuals identified with an abnormal gene for AAT, should be provided genetic counselling and offered testing for AATD For family testing after a proband is identified, AAT level testing alone is not recommended, because it does not fully characterise disease risk from AATD For diagnostic testing of symptomatic individuals, genotyping for at least the S and Z alleles is recommended Advanced or confirmatory testing should include Pi-typing, AAT level testing and/or expanded genotyping	Quantitative determination of AAT levels in blood is a crucial first test to identify AATD Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD Protein phenotyping by isoelectric focusing identifies variants where AAT is present in the sample including the rarer variants F, I and P, *etc.* Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants, where specific primers are available Gene sequencing remains necessary for those cases where a null variant or a deficient variant other than Z or S is suspected Testing of relatives of identified patients should be considered after appropriate counselling Genetic testing should be carried out only after informed consent is given and in accordance with the relevant guidelines and legislation
Pulmonary function testing		
	Initial evaluation with complete lung function testing is recommended Annual follow-up of adults with at least a spirometry test is recommended Since the lung disease associated with AATD often starts as purely parenchymal destruction, more complete pulmonary function testing (including measures of diffusing capacity) may be considered	Annual measurement of lung function including post-bronchodilator FEV_1 and gas transfer provides information about disease progression
Chest CT scanning		
	In newly diagnosed patients who are symptomatic and/or have abnormal pulmonary function testing, a baseline CT scan of the chest is recommended Serial chest CT scanning to monitor progression of disease is not recommended	Lung densitometry, as performed in observational cohort studies and randomised clinical trials, is the most sensitive measure of emphysema progression The correlation between change in lung density and any short-term change in measures of pulmonary function is weak; however, in the longer term, CT lung density decline correlates with reduction in FEV_1 and health status The role of CT in the follow-up of patients in routine clinical practice requires further validation

CT: computed tomography; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s.

Laboratory testing for AATD

According to the ERS statement [4], phenotyping remains a routine test for AATD, although it can only identify protein that is present in the blood. The laboratory diagnosis of AATD is usually performed by following two steps: determination of AAT concentration in serum or plasma (quantitative) and identification of allelic variants by phenotyping or genotyping (qualitative) [8]. In effect, the serum AAT concentration does not distinguish between normal and abnormal protein, but the abnormal protein can be identified using Pi phenotyping with an isoelectric gel [32]. If necessary, further testing should include gene sequencing which detects stop mutations and helps elucidate the nature of rarer variants such as E, F, G, I and P without the need for specific primers, as well as identifying currently unrecognised variants [4].

According to the US Alpha-1 Foundation, all individuals with COPD regardless of age or ethnicity, with unexplained chronic liver disease and with necrotising panniculitis, granulomatosis with polyangiitis, or unexplained bronchiectasis should be tested for AATD [31]. Parents, siblings and children, as well as extended family of individuals identified with an abnormal gene for AAT should be provided genetic counselling and offered testing for AATD. For family testing after a proband is identified, AAT level testing alone is not recommended, because it does not fully characterise disease risk from AATD. For diagnostic testing of symptomatic individuals, the US Alpha-1 Foundation recommends genotyping for at least the S and Z alleles. Advanced or confirmatory testing should include Pi-typing, AAT level testing and/or expanded genotyping [31].

According to the ERS statement [4], the quantitative determination of AAT levels in blood is a crucial first test to identify AATD. Quantitative deficiency must be supported by qualitative tests to identify the genetic mutation(s) causing AATD. Protein phenotyping by isoelectric focusing identifies variants where AAT is present in the sample including the rarer variants F, I and P, *etc*. Genotyping allows a rapid and precise identification/exclusion of S and Z alleles and other variants, where specific primers are available. Gene sequencing remains necessary for those cases where a null variant or a deficient variant other than Z or S is suspected. Testing of relatives of identified patients should be considered after appropriate counselling. Genetic testing should be performed only after informed consent is given and in accordance with the relevant guidelines and legislation.

The World Health Organization recommends that all patients with adult-onset asthma should be tested for AATD [33].

Using a cut-off of $\leqslant$85 mg·dL^{-1}, the serum AAT level identifies individuals with a PiZZ phenotype with a sensitivity of 99.5% and a specificity of 96.5%, but the sensitivity of this threshold to identify other phenotypes, such as PiSZ, is only 85.9% [32]. However, it must always be considered that AAT is an acute-phase protein that increases during infection and inflammatory states, which could lead to a missed diagnosis [31].

Pulmonary function testing in those with AATD

According to the US Alpha-1 Foundation, initial evaluation with complete lung function testing and annual follow-up of adults with at least a spirometry test are recommended. Since the lung disease associated with AATD often starts as purely parenchymal destruction, more complete pulmonary function testing (including measures of diffusing capacity) may be considered [31].

According to the ERS statement, annual measurement of lung function including post-bronchodilator FEV_1 and gas transfer provides information about disease progression [4].

Chest CT scanning in those with AATD

According to the US Alpha-1 Foundation, in newly diagnosed patients who are symptomatic and/or have abnormal pulmonary function testing, a baseline CT scan of the chest is recommended, whereas serial chest CT scanning to monitor progression of disease is not recommended [31].

According to the ERS statement, lung densitometry, as performed in observational cohort studies and randomised clinical trials, is the most sensitive measure of emphysema progression [4]. Although the correlation between change in lung density and any short-term change in measures of pulmonary function is weak, in the longer term, CT lung density decline correlates with reduction in FEV_1 and health status. The role of CT in the follow-up of patients in routine clinical practice requires further validation.

Augmentation therapy: advances and controversies

Current available therapeutic approaches to manage AATD includes lifestyle modifications such as smoking cessation, avoidance of environmental risks, nutritional follow-up, pulmonary rehabilitation and exercise, asthma and COPD pharmacological management including inhaled bronchodilators and steroids, antibiotics, oral corticosteroids, oxygen therapy, influenza vaccine and pneumococcal vaccine both conjugate and

polysaccharide as per guidelines. However, it must be mentioned that no trials reported the effects of typical treatments such as inhaled bronchodilators or combination therapy with inhaled corticosteroids, although there are data suggesting that influenza vaccination and self-management were at least suggestive of clinical benefit to AATD patients [34, 35]. Furthermore, because of the detrimental effect of smoke exposure on patients with AATD, immediate smoking cessation is mandatory at any stage of lung disease [36]. In any case, since uncertainty exists about the value of COPD treatments, further work is needed [37].

Augmentation therapy with intravenous purified AAT is central in the treatment of AATD, although lung volume reduction surgery and lung transplantation for emphysema associated with AATD could be considered [24] (table 2).

A meta-analysis published in 2009 suggested that exogenous AAT slows the loss of lung function seen in patients with AATD, with therapeutic benefit shown in patients with an FEV_1 30–65% pred and a need for further study in patients with mild (FEV_1 >65% pred) or very severe (FEV_1 <30% pred) airways obstruction [38]. However, in the same year, the EXACTLE study showed that CT has a higher sensitivity index score than lung function parameters, exacerbation frequency and quality of life, as determined by the St George's Respiratory Questionnaire [39].

Other studies published since 2010 have investigated the clinical efficacy of AAT therapy [40]. In particular, the RAPID-RCT/RAPID Extension (RAPID-OLE) trial [41, 42] is the largest randomised, placebo-controlled trial of AAT therapy completed to date. The RAPID was a multicentre, double-blind, randomised, placebo-controlled trial of AAT treatment in patients with AATD conducted over 2 years, in which patients were randomly assigned to receive AAT intravenously 60 $mg \cdot kg^{-1}$ per week or placebo for 24 months [41]. In the RAPID-OLE open-label extension, patients previously on placebo switched to AAT therapy and constituted the delayed-start group receiving only 2 years of active treatment by the end of RAPID-OLE, whereas patients who received AAT therapy in RAPID-RCT constituted the early-start group, receiving 4 years of active treatment [42].

Over 2 years of the RAPID-RCT study, a significant reduction in annual lung density decline rate was observed at total lung capacity (TLC), whereas results at functional residual capacity (FRC) alone or at TLC+FRC did not reach statistical significance. This difference was explained by higher measurement error in CT scans at lower lung volumes [41]. Patients who started 2 years of treatment after receiving placebo for 2 years (delayed-start group), had a similar rate of lung density loss between months 24 and 48 as patients who had received 4 years of active treatment (early-start group), showing a consistent treatment effect (*e.g.* similar rates of treatment benefit) [42]. Between day 1 and month 24, the annual decline rate at TLC was 33% higher in delayed-start patients compared to early-start patients. In addition, treatment efficacy of AAT therapy was maintained over 4 years in the early-start group. Furthermore, the trial showed that, between months 24 and 48, the delayed-start group did not regain the lung tissue that had been lost during the previous 2 years while on placebo, showing the importance of early intervention with AAT treatment.

The exogenous administration of purified human serum-derived AAT is the only approved specific treatment for AAT-deficient subjects with evidence of respiratory disease, but there are some characteristics for the optimal augmentation therapy [43]. The human serum-derived AAT must have high functional activity, must be sterile (free of known or unknown infectious particles) and pure (free of other proteins), with a low volume and salt content, must have low cost and a long half-life, must allow non-invasive administration and no need for mixing.

According to the US Alpha-1 Foundation [31], intravenous augmentation therapy in those with genetically confirmed AATD is recommended for individuals with an FEV_1 ⩽65% pred and for those with necrotising panniculitis. For patients with lung disease related to AATD and FEV_1 >65%, there is need for a discussion with each individual regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit, although a subanalysis of the RAPID-RCT trial suggests that AAT therapy is effective at all levels of FEV_1 impairment, and that treatment is therefore beneficial in both early- and late-stage disease [44]. In contrast, intravenous augmentation therapy is not recommended for individuals with the MZ genotype of AATD, those with lung disease due to AATD who continue to smoke and individuals with AATD and emphysema or bronchiectasis who do not have airflow obstruction. Furthermore, this therapy is not recommended for treating liver disease due to AATD or individuals who have undergone liver transplantation.

In effect, augmentation therapy is not indicated in AAT deficient patients with hepatic disease, because the liver involvement results from the accumulation of loop-sheet polymers of mutant ZAAT in the endoplasmic reticulum of the hepatocytes, a process that will continue even if the plasma level of AAT is augmented [43].

TABLE 2 Management of alpha-1 antitrypsin deficiency (AATD) in the adult according to the recommendations of US Alpha-1 Foundation [31] and European Respiratory Society (ERS) [4]

	US Alpha-1 Foundation	ERS
Augmentation therapy		
	Intravenous augmentation therapy is recommended for: individuals with FEV_1 ⩽65% pred; in those with lung disease related to AATD and FEV_1 >65% pred, there is need for a discussion with each individual regarding the potential benefits of reducing lung function decline with consideration of the cost of therapy and lack of evidence for such benefit; individuals with necrotising panniculitis Intravenous augmentation therapy is not recommended for: individuals with the MZ genotype of AATD; individuals with lung disease due to AATD who continue to smoke; individuals with AATD and emphysema or bronchiectasis who do not have airflow obstruction; the treatment of liver disease due to AATD; individuals who have undergone liver transplantation Additional recommendations regarding dosing of intravenous augmentation therapy: weekly doses higher than the current US FDA-approved dose are not recommended; monitoring of trough AAT blood levels to evaluate the adequacy of AAT augmentation dosing is not recommended	Several randomised clinical trials in severe AATD have shown intravenous augmentation therapy to reduce the progression of emphysema as assessed by CT densitometry There is no evidence to support efficacy of AAT augmentation therapy in PiSZ, PiMZ or current smokers of any protein phenotype Clinical trials have used fixed doses of AAT determined by body weight; whether individualising dosage based on trough levels for each patient has any benefit requires confirmation
Lung volume reduction surgery and endoscopic bronchial valve placement		
		Surgical volume reduction and endoscopic bronchial valve placement may be considered in selected patients with AATD, but further studies are needed to confirm the role of such therapies The optimal results of these techniques are obtained when a careful appraisal of risks and benefits are performed by a multidisciplinary team experienced in lung volume reduction and AATD
Lung transplantation		
		The survival benefit of lung transplant in AATD patients is not clear In general, patients with AATD have improved quality of life following lung transplantation Referral timing, rate of decline in lung function, health status and social support differ from patient to patient, and will have an influence on the evaluation for transplant The role of post-transplant augmentation therapy in particular needs to be explored

FEV_1: forced expiratory volume in 1 s; US FDA: United States Food and Drug Administration; CT: computed tomography.

According to the ERS statement [4], there is no evidence to support efficacy of AAT augmentation therapy in PiSZ, PiMZ or current smokers of any protein phenotype.

With regard to the correct dosing interval, only the 60 mg·kg^{-1} weekly dose has been shown to consistently maintain AAT serum levels above the 11 μM (57 mg·dL^{-1}) threshold, whereas serum AAT levels have been shown to decrease below 11 μM 1–2 days prior to the next dose with 120 mg·kg^{-1} every 2 weeks [40]. Longer dosing intervals may be beneficial in certain situations, *e.g.* to cover vacations, because higher doses are not associated with increased adverse events.

A recent European expert survey has shown that provision of AAT therapy is highly variable throughout Europe [45]. France and Germany were reported to have the highest proportions of diagnosed AATD patients receiving AAT therapy (60%); in Spain, ∼20% of patients receive treatment with AAT. When interviewees were asked their opinion on practical difficulties with AAT infusions and concerns regarding AAT doses >60 mg·kg^{-1} per week, practical challenges with AAT infusions were reported, the most often cited being infusion time (33%). The majority (73%) would consider alternative dosing strategies (*e.g.* bi-weekly dosing to cover holidays and for individuals in full-time employment). Most respondents would consider providing AAT doses higher than the recommended weekly dose of 60 mg·kg^{-1} when the "protective threshold" for AAT serum level was not reached, during exacerbations and for patients with rapidly deteriorating disease. The main concern regarding higher doses was the lack of proven clinical efficacy. With regard to physician perspectives on the most useful methods for monitoring AATD, quantitative CT of the lungs, *i.e.* measurement of lung density, was viewed as the most useful measure in clinical trial settings. D_{LCO} was considered the most useful measure for monitoring AATD in routine clinical practice, but less useful in clinical trials. Most physicians surveyed would consider using AAT therapy in patients with moderate disease severity, *i.e.* FEV_1 <80% and ⩾35% pred. A minority would consider AAT in early- and late-/end-stage disease (FEV_1 ⩾80% and <35% pred). Some physicians commented that in patients with severe AATD and FEV_1 above the historically recommended range for treatment (FEV_1 35–60% pred), quantitative CT should be used to confirm the presence, severity and distribution of emphysema. Self-administration of intravenous AAT was not available in any of the countries surveyed. However, all respondents would consider self-administration for some patients if it were available. For patients to self-administer independently, three training sessions provided by hospital-based respiratory nurses would be required.

Clinical trials have used fixed doses of AAT determined by body weight. Whether individualising dosage based on trough levels for each patient has any benefit requires confirmation, although it is known that subjects with AATD on the recommended standard dose (60 mg·kg^{-1} per week) augmentation therapy still exhibit inflammation, protease activity and elastin degradation that can be further improved by normalising AAT levels [46]. The results of a very recent pilot study that has explored the biological effects of double-dose AAT augmentation therapy suggest that this higher AAT dosing than currently recommended may lead to enhanced clinical benefits and should be explored further [46].

Surgery for patients with AATD

According to the ERS statement [4], surgical lung volume reduction and endoscopic bronchial valve placement may be considered in selected patients with AATD, but further studies are needed to confirm the role of such therapies. The optimal results of these techniques are obtained when a careful appraisal of risks and benefits are performed by a multidisciplinary team experienced in lung volume reduction and AATD. However, lung volume reduction is not recommended by the Alpha-1 Foundation guidelines for the management of AATD [31], although it has been suggested that individual emphysema morphology should be taken into account before dismissing lung volume reduction as a treatment option, as AATD patients with markedly heterogeneous emphysema may benefit more than others [47]. The endoscopic bronchial valve placement, being a less invasive procedure, could be considered in presence of homogenous emphysema [48].

The survival benefit of lung transplant in AATD patients is not clear. In general, patients with AATD have improved quality of life following lung transplantation. Referral timing, rate of decline in lung function, health status and social support differ from patient to patient, and will have an influence on the evaluation for transplant. In any case, a recent retrospective review of the data of all recipients with COPD and AATD transplanted at a single Irish centre reported that the median survival was 10.9 years in the AATD group and 8.1 years in the COPD group, with no statistical difference in FEV_1 decline at year 1, 5 and 10 between groups [49]. In any case, it can be argued that for end-stage lung, the bilateral transplant is the only chance of survival. It must be taken into account that AATD patient usually are younger that their common COPD counterparts, and the effect of AATD on the transplanted lungs is slow.

In particular, the role of post-transplant augmentation therapy needs to be explored, although the aforementioned retrospective review suggested a possible link between timing of withdrawal of

augmentation therapy and anastomotic complications, probably because increased neutrophil activity may occur as a rebound phenomenon following withdrawal of treatment with AAT [49]. In any case, a web-based survey showed that only 25% of lung transplant centres provided AAT replacement prior to, or following lung transplant in patients with known AATD, with lung transplant centres in North America replacing AAT (31%) more frequently than European lung transplant centres (9%) [50].

Liver transplantation is the only curative measure in patients with liver disease. For patients who develop liver failure, transplantation with a normal liver will provide normal levels of AAT; however, little is known about whether liver transplantation can prevent or delay the onset or progression of lung disease. It has been suggested that liver transplantation, and subsequent normal secretion of AAT, may halt progression of emphysema related to AATD [51].

Combined lung–liver transplant may be the only therapeutic choice in cases of end-stage emphysema complicated by cirrhosis in which the patient will probably not survive if only lung transplantation is undertaken [52].

Ongoing research and future treatments

The ERS statement [4] has indicated several new lines of research in AATD. There is a need to identify biomarkers of emphysema progression in AATD and biomarkers of response to augmentation therapy. Research on the minimum clinically important difference in rate of decline in lung density as a tool to assist clinicians and researchers in understanding the results of therapy is urgent. There is also the need to develop specific patient-reported outcomes for patients with emphysema associated with AATD. With regard to the therapy, research on the personalised augmentation therapy, with individualised selection of therapeutic regimen according to the patient needs, is a must. However, there is a great interest in developing genetic and regenerative therapies and other types of treatment, such as biochemical inhibitors of neutrophil proteinases. As already mentioned, efficacy of augmentation therapy after lung transplant in AATD patients must be explored.

In any case, areas for future research include also the need to identify an average terminal lung density threshold in AATD and emphysema to help quantify treatment advantage with AAT therapy [40]. Efforts should focus on identifying the optimal dosage/dosage interval and further study is required to confirm efficacy of AAT therapy in both early- and late-stage disease suggested by the RAPID-RCT data.

One of the main disadvantages of the AAT therapy is that intravenous AAT arrives at the lung in a relatively inactive state [53]. In order to improve AAT replacement therapy, the use of the inhaled route is an interesting possibility, because it targets the organ of interest directly, requires significantly less material to inhibit neutrophil elastase and, by lowering the amount of protein required, it reduces the cost of therapy [54]. However, the inhaled route needs to access the alveolar space that is destroyed in emphysema, and furthermore, it is not yet known whether the antineutrophil elastase capacity of inhaled AAT in the airspaces is sufficient to stop, improve or slow the progression of bronchiectatic and emphysematous lung disease [55]. To bring inhaled AAT to patients, placebo-controlled randomised phase 3 trials in well-defined and sufficiently large patient populations are necessary [54].

Considering that the AAT coding sequence is relatively short and the protein appears to function primarily in the plasma and extracellular space, which means that AAT production from any cell or tissue capable of secreting it could be useful therapeutically for augmentation, an alternative strategy is to develop gene therapy using multiple different vector systems, such as nonviral gene transfer making use of cationic liposomes, γ-retrovirus, recombinant adenovirus and recombinant adeno-associated virus vectors to express AAT [55, 56]. These approaches may be targeted to the lung epithelium as well as to hepatocytes, pleural and muscle cells. The challenge is to achieve long-term expression of large quantities of AAT.

It will be also important to define the real role of augmentation therapy with "normal" levels of serum AAT in the presence of high inflammatory diseases, related to neutrophil activation, such as bronchiectasis or lung transplantated patients (functional deficiency), and considering the evidence that suggests the broad effects of AAT on neutrophil functions [57] and, more generally, that AAT is a multifunctional pan-antiprotease, anti-inflammatory, immunomodulatory, anti-infective and tissue-repair molecule [58]. Since inflammaging is damaging and may be a factor in the pathogenesis of many ageing-associated diseases [59], the anti-inflammaging function of AAT documented in *Drosophila* as well as DNA damage-induced senescent cells suggest that AAT is an encouraging possibility to fight ageing and ageing-related diseases [60].

There are several novel approaches to the liver disease associated with AATD that are under preclinical investigation [55]. It has been suggested to modify pathways and proteostasis networks that are activated

by ZAAT polymers using pharmacological intervention able to reduce intracellular inclusions and/or increase the secretion of the mutant protein. Stimulating autophagy to clear intracellular inclusions with drugs such as carbamazepine, lithium and rapamycin that are able to decrease the hepatic load of ZAAT and hepatic fibrosis is another possibility. In addition, the use of small interfering RNA constructs targeted against hepatocyte mRNA encoding human AAT has been suggested to silence the expression of ZAAT. Alternatively, the development of novel strategies aimed to block intracellular polymerisation should be investigated further, considering that initial studies showed that peptides that are homologous to the reactive centre loop can bind to AAT and block polymerisation *in vitro*, and smaller peptides were identified that had a similar effect but with greater specificity for ZAAT, rather than the wild-type MAAT. Monoclonal antibody technology has allowed the identification of antibodies that detect the polymeric and latent conformers of AAT and antibodies that can block the transition of ZAAT to aberrant polymers without compromising inhibitory activity of the protein and increase its secretion. Furthermore, cell therapy for AATD using hepatocytes that express wild-type AAT seems to be an exciting possibility.

The ERS Assembly 5 (airway diseases, asthma and COPD) has created the European Alpha-1 Research Collaboration (EARCO) that is a clinical research collaboration with the aim to establish a collaborative effort that brings together multiple stakeholders, including researchers, healthcare providers, patients and industry, in order to advance understanding through clinical and scientific research and improve the quality of life of patients with AATD [61]. This pan-European initiative will enable a group of experienced and new researchers across Europe to answer fundamental questions about the epidemiology, genetics, physiopathology, clinical management and prognosis of lung disease associated with AATD.

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