Nine controversial questions about augmentation therapy for alpha-1 antitrypsin deficiency: a viewpoint

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Controversies about augmentation therapy in AATD still exist. Owing to the low prevalence of AATD and variability in its natural history, augmentation must be personalised in reference centres after careful consideration of pros and cons with the patient. https://bit.ly/409SwOs

Cite this article as: Miravitlles M, Anzueto A, Barrecheguren M. Nine controversial questions about augmentation therapy for alpha-1 antitrypsin deficiency: a viewpoint. *Eur Respir Rev* 2023; 32: 230170 [DOI: 10.1183/16000617.0170-2023].

Received: 22 Aug 2023
Accepted: 16 Oct 2023

Abstract

Augmentation therapy with intravenous alpha-1 antitrypsin is the only specific treatment for alpha-1 antitrypsin deficiency (AATD)-associated emphysema. This treatment has been available and remained basically unchanged for more than 35 years, but many questions persist regarding its indications, regimen of administration and efficacy. Because AATD is a rare disease, it has not been possible to conduct randomised, placebo-controlled trials that are adequately powered for the usual outcomes analysed in non-AATD-related COPD, such as lung function decline, exacerbations, symptoms or quality of life. New outcomes such as lung densitometry measured by computed tomography are more sensitive for identifying emphysema progression but are not widely accepted by regulatory agencies. In addition, clinical manifestations, severity and the natural history of lung disease associated with AATD are very heterogeneous, which means that individual prediction of prognosis is challenging. Therefore, the indication for augmentation is sometimes a dilemma between initiating treatment in individuals who may not develop significant lung disease or in whom disease will not progress and delaying it in patients who will otherwise rapidly and irreversibly progress.

Other areas of debate are the possible indication for augmentation in patients with severe AATD and respiratory diseases other than emphysema, such as bronchiectasis or asthma, and the use of therapy after lung transplant in AATD patients. All these uncertainties imply that the indication for treatment must be personalised in expert reference centres after in-depth discussion of the pros and cons of augmentation with the patient.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a relatively rare genetic disorder that results in reduced alpha-1 antitrypsin (AAT) concentrations in serum and, therefore, a reduction in anti-elastase activity in the lungs and increased risk of pulmonary emphysema [1]. The severe deficiency is usually caused by homozygous inheritance of the Z variant of the *SERPINA1* gene and is called proteinase inhibitor (Pi) *ZZ. It is estimated that from one in 3000 to one in 5000 individuals of European descent may have the Pi*ZZ genotype [2] and around one out of 850 cases of COPD in Europe [3] and one in 1300 in the USA [4] may be associated with AATD.

This deficiency was described in Sweden in 1963 [5] and the first and only specific treatment was developed in the USA in the 1980s. This treatment is based on the intravenous infusion of AAT purified from plasma donors, so-called augmentation therapy (AT) [6]. The half-life of the infused protein is 4.4 days and, therefore, the recommended regimen requires weekly infusions of human AAT throughout life to increase anti-elastase activity and prevent the progression of emphysema [6].

Despite the more than 30-year history of AT, there is still controversy about its clinical efficacy, basically due to the limited evidence from large placebo-controlled randomised clinical trials (RCTs). Furthermore, owing to the great variability in the severity and evolution of emphysema in AATD patients [7], there are some uncertainties about whom and when to treat [8], and whether patients with respiratory diseases other than emphysema or genotypes other than Pi*ZZ or null variants should also receive treatment [9–11]. Even the available guidelines regarding AATD frequently disagree in management recommendations [12].

Efficacy of AT

In the late 1980s, AT was approved by the US Food and Drug Administration based on the demonstration of its biochemical efficacy in restoring anti-elastase activity in serum and bronchoalveolar lavage fluid [6]. It was perceived that an adequately powered, prospective, placebo-controlled RCT to demonstrate the efficacy of this treatment in preventing the accelerated decline in lung function would not be feasible [13].

To overcome this problem, the National Heart, Lung, and Blood Institute (NHLBI) designed a prospective registry that followed 1129 patients on and off treatment for 5 years [14]. This registry demonstrated a significant reduction in the rate of decline in forced expiratory volume in 1 s (FEV_1) in patients receiving AT with a baseline FEV_1 between 35% and 49% predicted and a significant reduction in mortality in those receiving AT with an FEV_1 <50% predicted.

The second strategy was to look for an efficacy outcome other than lung function decline. It has been demonstrated that lung densitometry measured by computed tomography (CT) is more sensitive than FEV_1 % predicted to detect the progression of lung disease in AATD [15, 16]. Therefore, significant effects of AT could potentially be demonstrated with much smaller-scale RCTs [17].

The pooled analysis of two small placebo-controlled RCTs, including 54 and 77 patients each, demonstrated a significant reduction in the rate of decline of lung density with AT of 2.97 $g \cdot L^{-1}$ in 2 years [18]. Later, the largest RCT to date, including a total of 180 patients, also demonstrated a significant reduction in the rate of decline in lung density measured at total lung capacity, with a difference of 0.74 $g \cdot L^{-1} \cdot year^{-1}$ with AT *versus* placebo [19]. To put this into perspective, this change in lung density is like the average decline in lung density experienced by a patient with usual smoking-related COPD in 1 year (1.13 $g \cdot L^{-1}$) [20]. Conversely, AT does not treat symptoms, and we should not expect improvements in the usual outcomes evaluated in non-AATD-related COPD, such as the degree of dyspnoea, lung function, health-related quality of life or exacerbations. A systematic review of the evidence of AT efficacy is beyond the scope of this article, but it has been addressed in a recent publication [21] and in the European Respiratory Society (ERS) statement on AATD [22].

Current indications for AT

Indications for AT can be summarised as the demonstration of emphysema in a non-actively smoking patient with severe AATD; however, in most cases the different degrees of severity of the respiratory disease or rates of progression are not considered (table 1).

The heterogeneous manifestation of AATD and the extreme difficulty in establishing an individualised prognosis has led to great variability in clinical practice [7, 35]. A recent international survey among healthcare providers dedicated to AATD presented groups of three prescribers with the same hypothetical case; the three physicians agreed on the prescription of AT in only 58% of cases [8], and very often they recommended off-label use of AT not according to the current guidelines.

Therefore, taking all of the above into account, we selected the following nine questions about AT that remain controversial (table 2).

Question 1: Is there a threshold of AAT serum levels to indicate AT?

In a recent survey of 63 experts from 13 countries, the AAT serum level was the second most important criterion to initiate AT, only after AAT genotype [8]. The summary of product characteristics (SmPC) of the available products state that they are indicated for “severe” AATD, without any indication of the definition of severe in terms of serum levels [30, 31], and some guidelines suggest a protective threshold of <50 $mg \cdot dL^{-1}$ [24–26, 28] or <57 $mg \cdot dL^{-1}$ [27] or <11 μM [23]. Basically, the concept of AT is to increase serum levels above the protective threshold throughout the whole period between consecutive doses. Considering this principle, no individual with AAT serum levels >11 μM (or 50 $mg \cdot dL^{-1}$ or 57 $mg \cdot dL^{-1}$) should receive AT, because their serum levels are already above the therapeutic goal.

TABLE 1 Criteria for initiation of and approved indications for the products available for augmentation therapy (AT)

Guidelines and SmPCs	Recommendations
US guidelines [1]	Severe AATD in individuals with FEV_1 <65% predicted. In individuals with FEV_1 >65% predicted they recommend discussion about benefits and costs.
Canadian guidelines [23]	Non-smoking patients with COPD (FEV_1 25–80% predicted) attributable to emphysema and serum AAT <11 μM.
Belgian guidelines [24]	Non-smoking patients with AAT <50 mg·dL^{-1} and FEV_1 30–60% predicted and decline in FEV_1 % pred of >0.5% per year. Also patients with FEV_1 60–80% predicted if decline is >1% per year.
Spanish guidelines [25]	Age >18 years, non-smoking patients with AAT <50 mg·dL^{-1}, emphysema by CT or lung function with FEV_1 <80% predicted. AT should not be discontinued even if FEV_1 falls below 25% predicted.
Argentinian guidelines [26]	Age >18 years, non-smoking patients with AAT <50 mg·dL^{-1}, emphysema by CT or lung function with FEV_1 <80% predicted. AT should not be discontinued even if FEV_1 falls below 25% predicted. Not recommended in PI*MZ and the majority of Pi*SZ except if they have AAT <50 mg·dL^{-1} and fulfil all other criteria.
Portuguese guidelines [27]	Age >18 years, COPD attributed to emphysema caused by AATD, serum level <57 mg·dL^{-1}, FEV_1 30–70% predicted, or if FEV_1 >70% predicted, a decline in FEV_1 >120 mL·year^{-1}. Individual decision in other cases and AT should not be discontinued in case of deterioration of lung function.
Polish guidelines [28]	Severe AATD, emphysema, non-smoking patients with AAT <11 μM, FEV_1 30–65% predicted or annual decline in FEV_1 >50 mL·year^{-1}.
Australian and New Zealand guidelines [29]	AT could be considered in non-smoking patients with AATD (conditional recommendation and low-quality evidence).
Prolastin SmPC [30]	Indicated for chronic AT in patients with documented severe AATD (*e.g.* genotypes Pi*ZZ, Pi*Z (null), Pi* (null.null) and Pi*SZ). Patients must be on optimal pharmacological and non-pharmacological treatment and show signs of progressive pulmonary disease (*e.g.* reduced FEV_1, impairment in walking distance or increasing number of exacerbations), as evaluated by a healthcare provider with experience in AATD treatment.
Respreeza SmPC [31]	Indicated to reduce the progression of emphysema in adults with documented severe AATD (*e.g.* genotypes Pi*ZZ, Pi*Z (null), Pi* (null.null) and Pi*SZ). Patients must be on optimal pharmacological and non-pharmacological treatment and show signs of progressive pulmonary disease (*e.g.* reduced FEV_1, impairment in walking distance or increasing number of exacerbations), as evaluated by a healthcare provider with experience in AATD treatment.
Glassia SmPC [32]	Indicated for chronic AT and maintenance therapy in individuals with clinically evident emphysema due to severe hereditary alpha-1-Pi deficiency.
Zemaira SmPC [33]	Indicated for chronic AT and maintenance therapy for adults with alpha-1-Pi deficiency and emphysema.
Alfalastin SmPC [34]	Indicated in replacement therapy for adults with severe forms of primary AATD, phenotype Pi*ZZ or Pi*SZ, with pulmonary emphysema. The treatment is to be implemented as soon as possible after the first signs of emphysema. It is to be continued either continuously, especially in case of highly progressive emphysema, or through discontinuous cycles during episodes of bronchopulmonary infections.

AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; CT: computed tomography; ERS: European Respiratory Society; FEV_1: forced expiratory volume in 1 s; Pi: proteinase inhibitor; SmPC: summary of product characteristics.

It is important to consider that thresholds are relative; the risk of lung disease may not be different in patients with serum AAT levels of 49 mg·dL^{-1} or 51 mg·dL^{-1}, despite being at both sides of the threshold. Moreover, the discussion about the right threshold being 50 or 57 mg·dL^{-1} is clinically useless, because the difference between them is within the range of the natural variability of the measurement. Moreover, AAT is an acute phase protein that may increase in several different clinical circumstances, *e.g.* acute inflammation, infection or during pregnancy. These reasons are probably why most experts prefer to use the genotype, which is invariable, instead of using AAT serum levels as the main criterion to determine initiation of AT [8]: AT is indicated in Pi*ZZ or null genotypes and not in Pi*MZ and Pi*SS. In the case of Pi*SZ, AAT serum levels may be important, and in the few cases in which they are <50 mg·dL^{-1} (or 11 μM), in addition to the other criteria, AT could be indicated. However, this situation would only apply to a minority of approximately 5% of Pi*SZ patients [36]; moreover, in most cases, the clinical expression of lung disease in Pi*SZ individuals is more like Pi*MZ than Pi*ZZ [37, 38].

Question 2: When should AT be initiated?

The decision about when to initiate AT is not easy for different reasons: 1) AT is an intravenous treatment for life, without criteria for success or failure; 2) it is not an urgent treatment, the progression of emphysema is very slow and most of the harm is probably caused before diagnosis, when preventive actions such as smoking cessation and optimised treatment of COPD had not yet been initiated; but 3) on the other hand AT slows the progression of emphysema and, consequently, the earlier it is started in the

TABLE 2 Nine controversial questions about augmentation therapy (AT) and proposed answers

Question	Why this question?	Proposed answer
1. Is there a threshold of AAT serum levels to indicate AT?	The widely accepted protective threshold is 11 μM, although there may be variability between subjects.	It is better to initiate AT based on genotype and clinical characteristics than in AAT serum levels.
2. When should AT be initiated?	Criteria for AT are very wide and may include patients that may not always benefit from AT.	**The decision to initiate AT should be made by expert teams** after careful evaluation of clinical and functional characteristics and a pros and cons discussion with the patient.
3. Which is the right therapeutic dose regimen?	The approved dose regimen is 60 mg·kg^{-1}·week^{-1}, but infusions are also prescribed every 2, 3 or 4 weeks.	The most appropriate dose regimen is weekly administration, although two-weekly administration of 120 mg·kg^{-1} can achieve appropriate trough serum levels in most patients. **Three-weekly and monthly administrations are not recommended.**
4. Is AT indicated in patients with very severe disease?	After the initial findings from the NHLBI suggesting lack of effect of AT on rate of decline in FEV_1 in patients with FEV_1 <30% predicted, some guidelines do not recommend AT in these patients.	**Yes, it is indicated in this patient group.** The NHBLI study suggested increased survival in patients receiving AT. **FEV_1 decline is not a sensitive outcome in severe disease**.
5. Is AT indicated in patients with Pi*SZ or Pi*MZ genotypes?	Data from clinical registries show that an increasing number of Pi*SZ and even Pi*MZ patients are treated with AT.	**AT is not indicated in Pi*MZ and in most Pi*SZ patients**. More evidence is needed about the efficacy of AT in Pi*SZ.
6. Is AT indicated in patients with AATD and bronchiectasis?	There is increasing elastase burden in the lungs of bronchiectasis patients.	**AT is not currently indicated in bronchiectasis**. There is no evidence of clinical efficacy, or of efficacy in the prevention of exacerbations. More evidence is needed regarding inhaled AT in bronchiectasis.
7. Is AT indicated in patients with AATD and asthma?	Diagnosis of asthma in AATD is frequent and AATD may be involved in the pathophysiology of asthma.	**AT is not currently indicated in patients with asthma.** AT has only demonstrated efficacy in reducing the rate of decline of lung density; no other significant effects on respiratory symptoms or exacerbations have been demonstrated.
8. Who should prescribe AT?	AATD is a rare disease, and the clinical evolution of each person is very difficult to predict. Thus, there is a great variability in the opinion of prescribers about when and how to treat.	**Prescription of AT should be supervised by accredited reference centres.**
9. Is AT indicated after lung transplant?	The imbalance between proteases/antiproteases persists after lung transplant.	There are some reports of the beneficial impact of AT on prevention of infections, preservation of the graft and on graft *versus* host disease; however, it cannot be recommended for general use due to very limited evidence.

Strong negative or positive views are highlighted in bold. AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; FEV_1: forced expiratory volume in 1 s; NHLBI: National Heart, Lung, and Blood Institute.

course of the disease the better; and 4) the evolution and prognosis of lung disease in individuals with AATD may be unpredictable: never-smoker non-index subjects (*i.e.* those identified through family or population screening) have the same survival as the general population, and even patients with established emphysema may be stable for many years with appropriate COPD treatment and by avoiding exposure to respiratory toxins, whereas others may have accelerated decline in lung function despite treatment.

A recent review of existing AATD management guidelines has observed frequent disagreements in recommendations (table 1) [12]. Some guidelines, such as the Belgium [24], Portuguese [27] and Polish [28] guidelines, introduce the rate of decline in post-bronchodilator FEV_1 % predicted as a criterion for initiation of treatment; similarly, the accelerated rate of decline in FEV_1 % predicted ranked third as a criterion for AT in the European Alpha-1 Research Collaboration (EARCO) survey, only after AAT serum levels and genotype [8]. However, there is no guidance as to how to measure decline; only taking two measurements one year apart may not be accurate because FEV_1 is subject to variability owing to the technique itself and temporary conditions of the patient and may not reflect real and persistent decline [35]. Moreover, if 3–4 years of follow-up are required to evaluate real decline, then the observed loss of lung function will be irreversible and the patient will start treatment in a much worse clinical situation, which may be unethical. In most cases, the rate of decline in clinical practice can only be

evaluated retrospectively, when historical spirometric data are available to calculate the rate of decline over the course of at least the previous 3 years [35].

In summary, the decision dilemma is between initiating AT in individuals who may not develop significant lung disease or in whom disease will not progress and in delaying it in patients who will otherwise rapidly and irreversibly progress.

An informed decision should consider aspects beyond the established criteria for AT, and age is a very relevant variable. For example, a patient who smoked 10 pack-years until the age of 30 and presents with emphysema and an FEV_1 of 60% predicted at the age of 35 may be a candidate for immediate initiation of AT, whereas if the same patient were 70 years old, treatment should be initiated only if evidence of an accelerated decline in either FEV_1 % predicted or diffusion capacity of the lung for carbon monoxide (D_{LCO}) can be documented, otherwise it could be delayed until such a decline is observed. This decision requires careful consideration to avoid negative discrimination by age.

The individualised indication for AT taking into consideration age, smoking consumption, FEV_1 and D_{LCO} % predicted and, in some cases, the rate of decline in lung function was previously proposed by STOCKLEY *et al.* [39] and implies that the indication of AT should be reserved to reference centres [40].

Question 3: Which is the right therapeutic regimen?

The on-label regimen of treatment is 60 $mg \cdot kg^{-1} \cdot week^{-1}$ based on a half-life of the infused protein of 4.4 days and the target of a trough serum level above 11 µM, which is considered the protective threshold [6]. Owing to the inconvenience of weekly intravenous infusions for life, other off-label regimens every 2, 3 or 4 weeks have been investigated. The first observation is the safety of AT, demonstrated by the lack of significant side effects even with the prolonged administration of large doses of 250 $mg \cdot kg^{-1} \cdot month^{-1}$ [41]. However, due to the pharmacokinetics of the protein, specifically its half-life, because the time between infusions is prolonged, trough serum levels frequently drop below the protective threshold during the last days of the interval between administrations and this would certainly occur in administrations every 3 or 4 weeks and less often in two-weekly administrations [42]. The clinical significance of spending a few days with AAT serum levels below the threshold is unknown, but evidence derived from the RAPID trial [19] indicates that accelerated progression of emphysema is related to lower trough AAT serum levels in a dose-response fashion.

The ideal regimen would be one that mimics the physiological conditions in non-deficient subjects and is able to persistently increase serum levels to those of normal Pi*MM individuals and even increase in response to inflammation. However, with the available treatments, the regimen of choice is the weekly administration of 60 $mg \cdot kg^{-1} \cdot week^{-1}$. Off-label treatments every 3 or 4 weeks cannot be recommended because they result in very low trough serum levels and for several days at the end of each treatment interval AAT serum levels are below the protective threshold [42]. Two-weekly administration of 120 $mg \cdot kg^{-1}$, although also off-label and not optimal, may be a good compromise in some patients with stable pulmonary disease if the burden of weekly visits to the centre for administration is very great [42]. It is of note that in the NHLBI registry, 51% of patients were initially on weekly administrations, but this percentage decreased to only 33% at the end of a 5-year study [43]. Similarly, two-weekly administration was considered by 73% of European experts participating in a recent survey [44] and this was the most frequent regimen in the EARCO international registry, being observed in 49% of the treated patients; only 18.4% of patients were on weekly administrations [45].

All the previous recommendations are based on a protective threshold of 11 µM, but this threshold is controversial. It has been suggested that healthy non-smoking individuals with AAT serum levels above this threshold do not have an increased risk of developing pulmonary emphysema [46], but it is not known whether the same threshold may be protective in patients with moderate or severe emphysema who experience frequent or severe exacerbations. A more detailed discussion about the protective threshold is beyond the objectives of this article but interested readers can find more information elsewhere [46–48].

Recent studies have demonstrated the impact of double doses of AT (120 $mg \cdot kg^{-1} \cdot week^{-1}$) on markers of inflammation [49], and a RCT with a treatment arm of 120 $mg \cdot kg^{-1} \cdot week^{-1}$ is currently ongoing [50]. It is very likely that the approach of using the same dose for every patient, irrespective of the severity and characteristics of lung disease, may not be the most appropriate [39]. There is evidence that never-smoker, non-index cases with AATD have normal survival without therapy [51], and it is intuitive that treatment doses that may prevent the progression of emphysema in a patient with mild disease without exacerbations may not be enough in a patient with severe disease with emphysema and bronchiectasis with frequent

exacerbations and hospitalisations [39]. However, it is of concern that up to 87% of respondents in the European survey would consider providing AAT doses higher than the approved dose in some situations, *e.g.* when the protective threshold of AAT serum levels was not reached, during exacerbations and for patients with rapidly deteriorating disease [44], without any evidence indicating how or to what level to increase the dose or supporting its efficacy. Therefore, until new evidence is available, no new recommendations about personalisation of AT can be formulated.

Question 4: Is AT indicated in patients with very severe disease?

The NHLBI registry showed a significantly different rate of decline in post-bronchodilator FEV_1 in augmented *versus* non-augmented subjects with FEV_1 between 35% and 49% predicted; therefore, the first American Thoracic Society (ATS)/ERS guidelines recommended AT in patients with FEV_1 between 35% and 60% predicted [46]. Consequently, other guidelines do not recommend AT in patients with very severe disease with FEV_1 <30% predicted [24, 27, 28]. These recommendations create the possibility of under-prescribing AT for patients with AATD and severe emphysema because they have not considered other aspects of the disease, such as 1) the rate of decline of FEV_1 is not constant during the evolution of COPD, it is faster in milder disease and almost nonexistent in very severe disease [15, 16]; however, 2) emphysema progresses even in patients with very severely affected FEV_1 % predicted, with a progressive loss of lung tissue in very severe emphysema demonstrated by CT densitometry [15, 16]; 3) although the decline in FEV_1 % predicted is not affected by therapy in very severe disease, decreased mortality was observed in patients with AT with FEV_1 <50% predicted [14]. Despite this evidence, only 40% of European experts would consider AT for patients with FEV_1 <35% predicted, which is of real concern [44].

Owing to the existing evidence of treatment efficacy in severe disease beyond the lack of effect on rate of decline in FEV_1, new guidelines and some SmPCs of existing products no longer include a lower limit of lung function in the indication for AT [1, 25, 26, 30, 31]. Moreover, the Spanish and Argentinian guidelines include a sentence that warns against discontinuation of AT when FEV_1 falls below 25% predicted [25, 26]. In summary, AT must not be restricted or discontinued in patients with very severe disease but requires an individualised decision considering the cumbersome treatment and the lifespan of the patient.

Question 5: Is AT indicated in patients with Pi*SZ or Pi*MZ genotypes?

Given that the objective of AT is to maintain trough serum AAT levels above 50 $mg \cdot dL^{-1}$ (11 μM), Pi*MZ and the majority of Pi*SZ individuals should not receive AT because their AAT serum levels usually exceed this concentration. The case of Pi*MZ has been extensively studied and these individuals do not have an increased risk of lung disease if they do not smoke [10, 52]. Regarding Pi*SZ, the risk of lung disease is more like that in Pi*MZ than Pi*ZZ individuals [37], and recent studies have demonstrated that, as a group, Pi*SZ individuals do not have decreased survival compared to PI*MM individuals [53]. However, there might be a few Pi*SZ patients, probably no more than 5%, with AAT serum levels below the protective threshold and rapidly progressing emphysema who could be considered for AT [36]; furthermore, patients with the Pi*SZ genotype are included in the approved indication of AT in SmPCs [30, 31], despite the lack of evidence of efficacy of AT in these patients [22]. Before widely advocating the use of AT in Pi*SZ, the requisite clinical trials should be conducted.

Question 6: Is AT indicated in patients with AATD and bronchiectasis?

The development of bronchiectasis has been associated with incompletely opposed neutrophil elastase activity and, furthermore, neutrophil elastase activity is also a biomarker of frequent and severe exacerbations and accelerated lung function decline in patients with bronchiectasis [54]. This predominant role of neutrophil elastase suggests that patients with AATD and, consequently, unopposed elastase activity might be at increased risk of developing bronchiectasis and that AT could prevent the progression of lung disease in patients with AATD and bronchiectasis. However, the prevalence of severe AATD in patients with bronchiectasis is not significantly increased compared to the general population [55, 56] and the frequency of bronchiectasis in patients with AATD-related COPD is not higher than that observed in smoking-related COPD. Parr *et al.* [57] reported a frequency of clinically significant bronchiectasis in only 27% in patients with AATD and a mean FEV_1 of 57.9% predicted; similarly, among 629 Pi*ZZ patients in the EARCO registry, 85% of whom had CT scans available, the frequency of bronchiectasis was 22% [45]. For comparison, in non-AATD-related COPD, Kim *et al.* [58] reported a frequency of 38% of bronchiectasis among 389 patients with a mean FEV_1 of 54% predicted, and Martínez-García *et al.* [59] reported a frequency of 57% in patients with a mean FEV_1 of 49% predicted.

COPD itself is a risk factor for the development of bronchiectasis in patients with frequent and severe exacerbations [60] and, therefore, it is difficult to establish whether the presence of bronchiectasis may be

primarily due to the lack of AAT or to the presence of emphysema and exacerbations. Moreover, the infrequent clinical presentation of bronchiectasis alone in AATD patients suggests that, similarly to COPD, bronchiectasis develops because of emphysema and exacerbations [61]. Consequently, AT is currently not indicated for the treatment of bronchiectasis in patients with severe AATD unless the patient fulfils the other criteria for treatment, especially the coexistence of significant and progressing emphysema.

Question 7: Is AT indicated in patients with AATD and asthma?

All series of AATD patients have shown a high frequency of asthma diagnosis. Up to 35% of patients in the NHLBI registry had asthma [14] and 14.1% of Pi*ZZ patients in the EARCO registry had an asthma diagnosis [45], but with coexistent emphysema in most cases [62]. Similarly, out of 757 participants in the Alpha-1 Foundation Research Registry, 44% reported a diagnosis of asthma, but 83% of the Pi*ZZ patients reporting asthma also reported a diagnosis of COPD [63]. Often patients with severe AATD first present with asthma-like symptoms [64]. In the follow-up of the Swedish birth cohort at the age of 26 years, up to 16% of the Pi*ZZ individuals had a diagnosis of asthma and 22% reported recurrent wheezing, but no patient showed chronic airflow obstruction at this young age [65]. Although AATD itself might predispose to airway hyperresponsiveness and participate in asthma pathophysiology by different mechanisms, the relationship between AATD and asthma and asthma exacerbations [66] is not clear and the frequency of deficient genotypes of AAT is not increased in series of patients with asthma [64, 67, 68].

In addition to the unclear role of AATD in the development of asthma, trials of AT have only demonstrated efficacy in reducing the rate of decline of lung density, with no other significant effects on respiratory symptoms or exacerbations. Moreover, the NHLBI registry showed that asthma did not lead to accelerated decline in lung function and AT was not more effective in preventing loss of lung function in those with asthma compared to those without [69]. As in the case of bronchiectasis, AT is not currently indicated in AATD patients with asthma and should be reserved for patients with emphysema, with or without associated asthma.

Question 8: Who should prescribe AT?

Specific treatments for rare lung diseases are often restricted to reference centres; even some treatments for frequent diseases, such as biologicals for severe asthma, are only prescribed in expert centres in some countries. However, AT can be prescribed without specific limitations in most countries, probably owing to the demonstrated excellent safety profile. Nevertheless, we have already described the difficulties in selecting the right patient and the right time to initiate AT, considering the balance between a late prescription with the associated irreversible lung damage and inadequate prescription that may result in dependence on an intravenous treatment for life (for no clinical benefit) and a high associated cost.

There is evidence of the inappropriate use of AT. In the USA, data reported in 2008 showed that of the 352 samples sent to the DNA Alpha-1 Foundation DNA and Tissue Bank with a Pi*MZ genotype, 23 patients (6.5%) were receiving AT at DNA donation [9]. Several members of the advisory committee of the Alpha-1 Foundation and the Alpha-1 Foundation Clinical Resource Centers cited awareness of instances in which Pi*MZ heterozygotes were receiving AT at the time of referral, often at the suggestion of a local pharmaceutical sales representative to a physician with little experience treating individuals with AATD [9]. However, this is not the only example of a possible misuse of therapy; there are reports of off-label initiation of AT in children [70] and pregnant women [71], which is surprising considering that AT cannot be considered an “urgent” treatment and initiation can be postponed to after delivery, if indicated.

Owing to the low prevalence of AATD, it is difficult for a single centre to accumulate experience in the care of these patients. As an example, of the 124 physicians reporting cases to the Spanish AATD registry, 71% reported only one or two patients, while only three physicians in the country reported more than 40 cases [72]. Therefore, it is not surprising that the European Council [73], the ERS [22] and the Alpha One Foundation guidelines [1] recommend organising the care of AATD patients in reference centres that can accumulate experience in management. Even the SmPC of Prolastin [30] and Respreeza [31] indicate that the treatment “must be evaluated by a healthcare provider with experience in the treatment of AATD”. Owing to the difficulties related to weekly travel to centres by patients living far away, mixed models of care can be established, with reference centres prescribing AT, following the patients annually and participating in international registries [45] and treatment provision through local healthcare institutions or home-based treatment and even self-administration of AT [44]. In any case, each patient who is a candidate for AT must be individually evaluated and a discussion between the patient and the healthcare provider on the pros and cons of AT and type of dispensation of therapy is necessary.

Question 9: Is AT indicated after lung transplant?

The common practice is to withdraw AT after lung transplant (LT), because the implantation of emphysema-free lungs reverses the main indication for receiving this treatment. Moreover, even if we take into consideration a possible increased risk of recurrence, emphysema in non-smokers could take several years or decades to develop. Nevertheless, LT patients may present with complications which differ from COPD, and this has raised the question of whether AT could have a role after transplantation [11].

Compared to non-AATD-related COPD, patients undergoing LT due to AATD have more favourable long-term outcomes, although a faster decline in FEV_1 has been reported in double LT AATD individuals compared to in COPD [74], as well as increased risk of complications mainly related to viral and fungal infections and graft failure [75–77].

Infection is a common complication in LT and may also contribute to acute rejection and the development of chronic lung allograft dysfunction. In AATD individuals, exacerbation episodes are associated with a greater degree of inflammation than in non-deficient patients [78], which could potentiate the deleterious effect that infections play on the graft. Indeed, King *et al.* [79] described an abnormal protease–antiprotease balance in bronchoalveolar lavage fluid after LT in AATD individuals, with newly developed free elastase activity during infection episodes, which was inhibited *ex vivo* by adding AAT. Interestingly, a withdrawal effect of therapy has been described in patients who discontinued augmentation: McElvaney *et al.* [80] reported a significant increase in the risk of exacerbations and hospital admissions after abrupt withdrawal of AT, and these events were associated with decreased anti-elastase activity and increased inflammatory biomarkers. The reported increased incidence of dehiscence in AATD LT recipients could also be associated with the withdrawal of AT after LT [76, 77]. Interestingly, Conrad *et al.* [81] found that patients who underwent LT for AATD and who were previously on AT had lower survival rates than patients who were untreated pre-LT; it is not known whether a withdrawal effect of treatment could be implicated in this unexpected finding.

Evidence on the use of AT post-LT is scarce and mainly comes from animal models. In murine models without AATD, AAT infusion after LT resulted in attenuation of the inflammatory infiltrate in the allograft and the risk of acute rejection [82, 83]. Treatment of 24-h *ex vivo* lungs with AAT infusion resulted in improved physiological function, reduced pulmonary oedema and inflammation, and decreased apoptosis in a swine model [84]. The retrospective experience of a single centre reported greater maintenance of lung function when AT was not discontinued after LT [85]. Despite these observations, more evidence is needed to support the continuation of AT after LT.

Conclusions

Although AT has been in use for more than 30 years, there is large variability in its use and there are still several uncertainties regarding its indication. A personalised approach to the indication and treatment regimen seems to be the most adequate, but there is a lack of evidence about aspects, such as the right protective threshold for each patient, the efficacy of different treatment regimens and the right outcome for evaluating the evolution of emphysema. Currently, there is no evidence for the treatment of Pi*MZ or Pi*SZ heterozygotes, or patients with AATD and bronchiectasis or asthma without significant or progressive coexistent emphysema. In this context, individualised prescription in reference centres with a discussion between the patient and the healthcare provider on the pros and cons of AT is necessary.

Provenance: Submitted article, peer reviewed.

Conflict of interest: M. Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols and Novartis; consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, ONO Pharma, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi, Zambon and Grifols; and research grants from Grifols. A. Anzueto has received consultant fees from AstraZeneca, Boehringer Ingelheim, Grifols, GlaxoSmithKline, Verona Pharma, TEVA and Mylan/Theravance. M. Barrecheguren has received speaker fees from Grifols, Menarini, CSL Behring, GSK and Boehringer Ingelheim; and consulting fees from GSK, Novartis, CSL Behring and Boehringer Ingelheim.

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