Treatment with inhaled α1-antitrypsin: a square peg in a round hole?

Miriam Barrecheguren and Marc Miravitlles

Affiliation: Pneumology Dept, Hospital Universitari Vall d'Hebron/Vall d'Hebron Research Institute (VHIR), Barcelona, Spain.

Correspondence: Marc Miravitlles, Pneumology Dept, Hospital Universitari Vall d´Hebron, P. Valld'Hebron 119-129. 08035 Barcelona, Spain. E-mail: marcm@separ.es

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α1-Antitrypsin deficiency (AATD) is a genetic disorder that predisposes to the development of early pulmonary emphysema, especially in smokers. Episodes of exacerbations are frequent in patients with emphysema due to AATD and are associated with a deficient antiprotease screen in the airways compared with that of non-deficient COPD patients [1]. As a consequence, exacerbations have great impact on the evolution of the lung disease in AATD, measured in terms of decline in gas transfer [2], in health status [2, 3], and in lung function over time [4, 5].

To date, the only specific treatment for AATD-related emphysema is the intravenous infusion of purified α1-antitrypsin (AAT) derived from plasma donors, so-called augmentation therapy. Previous randomised clinical trials (RCTs) have consistently shown the efficacy of augmentation therapy in slowing the progression of pulmonary emphysema measured by computed tomography densitometry in individuals with severe AATD [6, 7]. However, evidence of the effect of augmentation on exacerbations is very limited and comes exclusively from a couple of observational studies that described a reduction in the frequency of exacerbations in patients after initiation of therapy [8, 9]. The lack of effect of augmentation therapy on exacerbations observed in RCTs can be due to different reasons: 1) the studies were not powered for exacerbations; 2) the patient populations were not enriched for exacerbators; and 3) augmentation *per se* may not have an effect on the prevention of exacerbations, but may help to preserve lung integrity in case of an exacerbation.

Due to this lack of evidence from RCTs of the effect of augmentation on secondary outcomes such as exacerbations, dyspnoea or quality of life, this therapy is still not reimbursed in some countries [10]. This unfortunate situation is a consequence of the erroneous approach of evaluating the efficacy of an aetiological or disease-modification treatment (augmentation therapy) with the same outcome measurements as a symptomatic treatment (bronchodilators). Why should an intravenous antiprotease reduce exacerbation frequency or improve dyspnoea or the St George's Respiratory Questionnaire score? The objective of augmentation therapy is to prevent or stop the evolution of emphysema, and this has been already demonstrated in the existing RCTs [8, 9, 11].

However, treatment with AAT does not lack drawbacks. Therapy with AAT implies weekly intravenous infusions, it is time consuming and expensive, and is usually for life. Hence, there is interest in finding new treatments that may help reduce the progression and burden of the disease and that may be more convenient for patients. In this context, previous studies have shown that aerosol administration of AAT to

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patients with AATD was safe and feasible and resulted in a return to normal of anti-neutrophil elastase defences of the lower respiratory tract [12]. Inhaled AAT can also decrease the levels of elastase activity, neutrophils and pro-inflammatory cytokines in patients with cystic fibrosis [13] and can even decrease bacterial load in the respiratory tract in animal models [14].

Based on these observations, STOLK *et al.* [15] designed a double-blind RCT that aimed to demonstrate the effect of nebulised AAT on the reduction of exacerbations in patients with AATD. Both groups received 50 weeks of inhaled AAT or placebo twice a day. The results of the study showed no effect of AAT on time to first exacerbation compared to placebo. However, patients treated with inhaled AAT had a significant reduction in Anthonisen type I exacerbations (more symptomatic) and, interestingly, there was also a trend towards an improvement in forced expiratory volume in 1 s (FEV_1) in the treatment arm [15].

The first observation is that, despite being well designed and conducted, the trial encountered some issues that could have hindered the efficacy of therapy. The nebuliser device and medication dispensation were improved along the study based on feedback from patients, which significantly reduced the rate of adverse events in the AAT group by the end of the study [15]. Given the high percentage of adverse events and withdrawals, and considering that some adverse events may have mimicked exacerbations, it seems reasonable to think that having an optimised treatment from the beginning would have had a positive effect on the results of efficacy of inhaled AAT.

The selection of exacerbations as a primary outcome can pose a challenge of its own. Since there are different phenotypes of exacerbations, and emphysematous patients may experience pauci-inflammatory episodes [16, 17], the possible benefits of the antiprotease effect on the prevention of exacerbations in AATD are not clear. In fact, among those patients presenting at least one exacerbation during the trial (85%), almost half suffered a type III exacerbation (only one symptom), an increase in dyspnoea being the only symptom in around 80%. It is very unlikely to see an impact of an antiprotease treatment on exacerbations characterised only by an increase in dyspnoea captured in a diary. However, STOLK *et al.* [15] also observed a decrease of type I exacerbations with inhaled AAT and a reduction of type II exacerbations, particularly those characterised by increased sputum volume and purulence. These results suggest that the maximal effect of this therapy could be expected in patients with an infectious exacerbator phenotype similar to cystic fibrosis, or in those with associated bronchiectasis [18].

Another important consideration is patient selection. Patients were included if they had had at least two exacerbations, either moderate or severe, during the previous 18 months, with one having taken place in the last 12 months. This definition does not guarantee that patients suffered from frequent exacerbations, and in fact 25% of patients did not fulfil the standard definition of a frequent exacerbator, which may have lessened the margin of improvement with treatment [15]. Nonetheless, the difficulties in recruiting enough individuals with a particular phenotype in a rare disease such as AATD have to be recognised (*i.e.* frequent exacerbators), and, therefore, the authors must be acknowledged for trying their best to enrich their population with exacerbators as much as possible.

Unexpectedly, patients treated with inhaled AAT showed a rapid increase in FEV_1 of less than 50 mL after 4 weeks of treatment and maintained a mean difference of around 50 mL in FEV_1 throughout the study compared to placebo. Further analysis of FEV_1 decline without the data from the first 4 weeks, during which there was a "hockey stick effect" in the AAT group, suggested that the slope of decline of FEV_1 might be favourable to the AAT arm. It should be noted that FEV_1 was not even a secondary outcome and was evaluated only as a safety parameter and, therefore, these results should be interpreted with caution [15].

This pattern of improvement in lung function with inhaled AAT is similar to that observed with drugs such as inhaled corticosteroids (ICS) [19] or roflumilast [20], and suggests a local anti-inflammatory effect. Based on these findings, the authors defend the design of a new RCT with inhaled AAT using FEV_1 as the primary outcome. This is a very controversial proposal, because the alpha community has been struggling for decades to convince healthcare providers and regulators that, unlike non-AATD related COPD, FEV_1 is not an appropriate end-point for therapeutic trials in AATD, since the number of patients required to power a study for FEV_1 decline is unattainable in this rare disease [21]. Furthermore, lung densitometry has shown to be a much better parameter to assess both the evolution of emphysema and the efficacy of treatment in AATD [11, 22, 23]. Insisting again on efficacy trials in AATD with FEV_1 as primary end-point is a dangerous strategy that will very likely produce negative results and increase the confusion among patients, physicians and payers. In the best-case scenario, an improvement in FEV_1 within the range of less than 100 mL can also be obtained with other drugs such as ICS, which are less expensive and more convenient than inhaled AAT [24]. A possible lack of (or small) effect of AAT on FEV_1 should not mislead us from recognising the crucial effect of augmentation therapy in reducing the rate of destruction of lung parenchyma in emphysema associated with AATD [25–27].

The authors must be congratulated for designing and conducting an RCT that represents a completely new approach in the treatment of patients with emphysema due to AATD. This study was highly anticipated, and although the results were not as positive as we had all hoped, it has provided very valuable information. The trial has demonstrated that the inhaled route of administration of AAT is safe and feasible and has improved the inhalation device and technique of administration for subsequent studies. Although the results obtained do not support the use of inhaled AAT for the majority of patients with emphysema associated with AATD, they also suggest that a subgroup of patients, those with frequent infective exacerbations, and that present with increased sputum volume and purulence, may benefit from inhaled AAT in the form of a change to a milder type of episodes and probably even with increased protection against the long-term effects of recurrent exacerbations in the lungs. Future studies with this type of treatment approach should focus on this specific phenotype of AATD individuals and investigate whether this effect justifies the long-term use of twice daily inhaled AAT on top of optimised COPD therapy.

Conflict of interest: M. Barrecheguren has received speaker fees from Grifols, Menarini, CSL Behring, GSK and consulting fees from GSK, Novartis and GebroPharma. M. Miravitlles reports speaker's fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, TEVA, pH Pharma, Novartis and Grifols, and research grants from GlaxoSmithKline and Grifols, outside the submitted work.

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