Efficacy of augmentation therapy for emphysema associated with α_1-antitrypsin deficiency: enough is enough

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Augmentation therapy is effective in reducing the rate of decline of lung density in α_1-antitrypsin deficiency http://ow.ly/UXtMd

α_1-Antitrypsin deficiency (AATD) is an autosomal co-dominant genetic condition which is widely prevalent in populations of European descent [1]. The pathogenesis of AATD-related lung manifestations is related to a protease (namely neutrophil elastase)–antiprotease (*i.e.* α_1-antitrypsin, AAT) imbalance occurring in the respiratory system. In subjects with AATD this imbalance is usually caused by an enhanced burden of neutrophils, hence of neutrophil elastase, in the lung tissue, due to smoking and/or recurrent respiratory infections, and a variety of lung disorders may develop, predominantly lower lobe panacinar emphysema [2].

To restore the balance between proteases and antiproteases in the lung, there are basically two options: to lower the burden of proteases and/or increase the activity or the amount of antiproteases. 28 years ago, the team of the Pulmonary Branch of the National Institutes of Health in Bethesda (MD, USA) demonstrated the feasibility of increasing the amount of antiproteases in the lung to up to the protective threshold of 11 μM (0.49 $g{\cdot}L^{-1}$) by intravenous infusion of exogenous AAT weekly to patients with AATD [3, 4]. This seminal study was the first to demonstrate the biochemical efficacy of the so-called "augmentation therapy" for AATD. At that time, a decline in forced expiratory volume in 1 s (FEV_1) was considered the best marker of the evolution of emphysema, and a clinical trial aimed at demonstrating the efficacy in slowing disease progression using FEV_1 decline as the outcome measure was estimated to require 1000 patients per treatment arm followed for 3 years [5]. It was clear that such a trial was not feasible due to the low number of patients diagnosed with the disease and the extremely high costs involved. Therefore, augmentation therapy was approved by the US Food and Drug Administration in 1987 based on its biochemical efficacy, and it is used by a large number of patients in many countries, including many European countries, after having received approval by European health authorities.

However, the interest in demonstrating the clinical efficacy of augmentation therapy has not lessened. Large observational studies have been conducted whereby patients on continuous or intermittent augmentation therapy showed a slower decline in lung function and reduced mortality compared to those not receiving treatment [6, 7]. Nonetheless, investigators have been struggling to find an adequate outcome measure that could allow the design of a randomised placebo-controlled clinical trial (RCT) with a feasible sample size and follow-up time.

Received: July 15 2015 | Accepted after revision: Sept 2 2015

Conflicts of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

Is lung density an adequate outcome measure?

Emphysema due to AATD can be compared with osteoporosis. In both diseases, the main pathological event is the loss of the corresponding tissue. The main outcome in osteoporosis is the measurement of bone density by a validated imaging technique; therefore, the development and validation of an adequate measurement of lung density should include the most sensitive outcome measure of lung degradation in AATD.

Imaging techniques for the quantification of lung density were intensively developed using computed tomography (CT) at the beginning of the twenty-first century [8]. It has been demonstrated that lung density assessed by CT scans in emphysema due to AATD is associated with health-related quality of life [9] and is the best predictor of death (together with age) [10]. In addition, CT densitometry allowed the quantification of the annual loss of lung tissue and demonstrated that this loss was persistent over the whole spectrum of severity of lung disease, in contrast to FEV_1, the decline of which is almost nonexistent in severe chronic obstructive pulmonary disease (COPD) [11, 12].

In a small 3-year RCT with 30 patients per study arm, Dirksen *et al.* [13] used CT densitometry as a secondary outcome and demonstrated an almost significant reduction in the rate of decline in lung density with augmentation therapy (p=0.07). Power analysis showed that this protective efficacy would be significant in a similar trial including 130 patients.

Almost 10 years later another RCT showed a very similar effect of augmentation therapy in reducing the loss of lung density compared to placebo. Unfortunately, only 77 patients were included instead of the 130 suggested by the previous RCT, and therefore, the reduction in lung density was of borderline significance (p values ranged 0.049–0.084 according to the method of adjustment of densitometric analysis applied) [14].

Finally, the recently published RAPID trial has included 180 patients with emphysema associated with AATD recruited in 28 centres in 13 different countries, who were randomised to augmentation therapy or placebo and were followed for over 2 years by CT densitometry [15]. Since the time of observation was felt to be insufficient, the authors proposed an additional extension study in which patients were followed in open-label for another 2 years. The results again showed that augmentation therapy was effective in reducing the annual loss of lung parenchyma, being demonstrated by a statistically significant reduction of the loss of lung density measured at total lung capacity (TLC) of 34% (p=0.03). However, the results of RAPID may be difficult for clinicians to understand. One reason for this may be that the regulatory authorities asked the investigators to include the measurement of lung density at functional residual capacity (FRC), and measurement at FRC combined with TLC as three co-primary endpoints. Lung density at FRC has not previously been considered as an adequate outcome measure because measurement error is highest for CT scans obtained at the lowest lung volumes (*e.g.* FRC) [16], and therefore the sample size to obtain significant differences in measurements obtained at FRC would be significantly higher. In RAPID, the results at FRC and the combination of FRC and TLC also showed a reduced, albeit not significant, loss of lung density with active treatment (p=0.18 and p=0.06, respectively) [15]. Another potentially confusing finding is the lack of efficacy in secondary outcomes such as exacerbations, lung function or health status. As mentioned previously we know from trials in COPD that large sample sizes are necessary to demonstrate changes in lung function decline, exacerbation rates or health status; therefore, it is not surprising that an RCT such as RAPID with 90 patients per arm is clearly underpowered to see any effect of treatment (or even a trend) in any of these secondary variables.

In contrast, other results derived from RAPID highlight the efficacy of augmentation therapy. Patients initially in the placebo arm who agreed to continue in the extension period and therefore received augmentation therapy open-label for the next two years, showed a change (reduction) in their rate of decline in lung density that was similar to the decline observed in patients initially included in the augmentation therapy arm (figure 1) [15]. This result indicates that augmentation therapy reduces the rate of lung density decline from the start of therapy highlighting the need for early diagnosis and treatment of lung emphysema associated with AATD to prevent the accelerated loss of lung tissue. Second, a *post hoc* pharmacometric analysis showed that the annual rate of lung density loss was inversely proportional to the trough serum AAT concentrations achieved by augmentation therapy, with no evidence of a plateau within the range measured (p=0.03) [15]. This demonstration of a dose-response effect of augmentation therapy on the prevention of lung destruction is strong additional evidence supporting the efficacy of augmentation therapy.

What does reduction in the loss of lung density means?

Despite the reduction in the loss of lung density observed in the three RCTs mentioned above, the clinical meaning of this outcome in relation to the evolution of COPD is not generally understood. Data from patients included in the RAPID trial indicate that average lung density at lung transplantation or death was less than 19.0 $g{\cdot}L^{-1}$, and at baseline for enrolled patients it was 47.1 $g{\cdot}L^{-1}$ [15]. The time to terminal

DOI: 10.1183/13993003.01145-2015

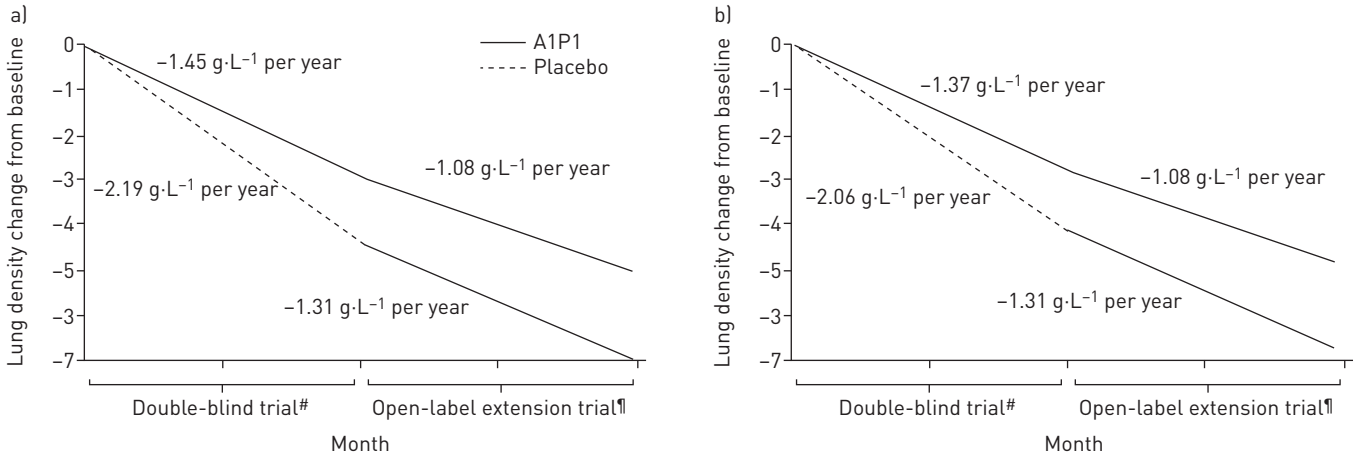

Figure 1 Rates of lung density decrease at total lung capacity during the double-blind and open-label portions of the trial in a) all patients and b) patients completing the open-label study only. Data are annual rates of decrease. A1PI: α_1 proteinase inhibitor. #: A1PI n=92; placebo n=85. ¶: A1PI n=50; placebo n=47. Reproduced from [15] with permission from the publisher.

respiratory function can be extrapolated from these two values of lung density and the rates of annual lung density decrease at TLC in the two treatment groups. The estimated time to terminal respiratory failure was 18.1 and 12.3 years in the augmentation therapy and placebo group, respectively [15].

In COPD, data from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study showed that the mean decline in lung density was1.13 g·L^{-1} (measured by CT at TLC) [17]. Therefore, the difference found in the annual decline of 0.74 g·L^{-1} described in augmentation therapy in RAPID was 65% of the mean yearly decline of lung density observed in COPD. The results of the ECLIPSE suggest that the decline in lung density could also be considered an important endpoint for COPD.

What are the consequences of the results of the RAPID trial?

First, we think that it is time to abandon the scepticism about augmentation therapy. The three RCTs performed to date have shown consistent results in the reduction of the rate of lung density decline with augmentation therapy compared with placebo (table 1), and there is currently enough information to understand the impact of this reduction in density on disease progression and prognosis.

Second, we need to ensure the availability of augmentation therapy to all patients fulfilling the criteria for this treatment [2, 19] under equal conditions [20]. In this respect, it should be taken into account that not all individuals with AATD develop the same degree of emphysema [21–24] and that indication of augmentation therapy should be individualised based on case-by-case evaluation by experts in reference centres [25].

TABLE 1 Lung density measurements in RCT with augmentation therapy in AAT

First author [ref.]	Year	Patients randomised	Treatment and duration	Decline in lung density at TLC	Difference
Dirksen [13]	1999	28 AAT and 28 placebo	250 mg·kg^{-1} AAT every 4 weeks for 3 years	Annual change: AAT −1.5 (SD 0.41) g·L^{-1}; placebo: −2.57 (SD 0.41) g·L^{-1}	1.07 (SD 0.58) g·L^{-1} per year (p=0.07)
Dirksen [14]	2009	36 AAT and 35 placebo	60 mg·kg^{-1} AAT every week for 2 years	Total change (2 years)#: AAT −2.36– −3.38 g·L^{-1}; placebo −3.81– −4.82 g·L^{-1}	Total difference (2 years)#: 1.47–1.59 g·L^{-1} (p values between 0.084 and 0.049#)
Stockley [18]	2010	Pooled analysis of previous RCTs. 60 AAT and 59 placebo	250 mg·kg^{-1} or 60 mg·kg^{-1} of AAT every 4 weeks or every week	Total change (2 years): AAT: −4.08 g·L^{-1}; placebo: −6.38 g·L^{-1}	Total difference (2 years): 2.29 g·L^{-1} (p=0.006)
Chapman [15]	2015	93 AAT and 87 placebo	60 mg·kg^{-1} of AAT every week for 2 years	Annual change: AAT −1.45 (SE 0.23) g·L^{-1}; placebo −2.19 (SE 0.25) g·L^{-1}	0.74 g·L^{-1} (p=0.03)

#According to the four different adjustments for evaluation of lung density performed in the study. TLC: total lung capacity; AAT: α_1-antitrypsin; RCT: randomised controlled trial; AT: augmentation therapy; SD: standard deviation; SE: standard error.

Third, we have to acknowledge the importance of patient associations and registries of AATD since patients are the main stakeholders of such orphan diseases. Indeed, as the main stakeholders, new studies have been fostered to definitively demonstrate the efficacy of augmentation therapy and registries have allowed the collection of data on the natural history of the disease [6, 7, 26, 27] and differences between phenotypes [22, 24, 28]. They also allow the identification of patients that could potentially be enrolled in RCT. Physicians and patients have to continue to work together to provide the best standard of care for individuals affected by this genetic disorder.

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DOI: 10.1183/13993003.01145-2015