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Alpha-1 antitrypsin (A_1-PI) treatment slows emphysema progression independent of baseline FEV_1

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Introduction

- Alpha 1 Antitrypsin deficiency (AATD) is a hereditary disorder, characterised by decreased levels of functional alpha 1 proteinase inhibitor (A_1-PI; also known as alpha 1 antitrypsin, AAT), which may lead to early-onset emphysema[1]
- Therapy with intravenous AAT has been shown to slow the decline of FEV_1, specifically in patients with FEV_1 30–65% at baseline[2,3]
  - These observational studies have failed to confirm a similar effect of AAT therapy in patients with baseline FEV_1 >65% and <30%
- This has resulted in a treatment recommendation for intermediate disease only (FEV_1 35–60% predicted),[4] when lung function decline is predicted to be greatest
- Computed tomography (CT) lung density, measured as volume-adjusted 15th percentile (PD15), is a more sensitive endpoint, and is also able to assess changes across the whole spectrum of emphysema severity
- In RAPID-RCT, a 2-year, randomised, double-blind, placebo-controlled study, 180 patients with a broad range of baseline FEV_1 were included and regularly followed for PD15 measurements[5]

Aim

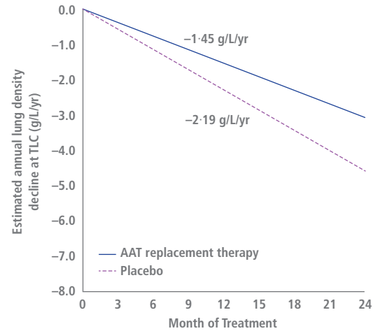
- To assess the correlation between change in PD15 and baseline lung functional status (FEV_1 % predicted, DL_{CO} and baseline-adjusted PD15) for placebo- versus AAT-treated patients

Methods

Measuring the change in lung density

- During RAPID-RCT, CT scans were taken at baseline and 12, 21 and 24 months
- Repeated CT scans at total lung capacity (TLC) and functional residual capacity were obtained and PD15 was calculated
  - A physiological volume correction was applied as previously described[6]
- In RAPID-RCT, a significantly lower annual rate of lung density (adjusted PD15 at TLC) decline was observed in patients treated with AAT versus placebo (**Figure 1**; p=0.033)[5]
- For this *post-hoc* analysis, PD15 values were calculated for scans taken at TLC only; to assess treatment effects, 2-sided tests were applied

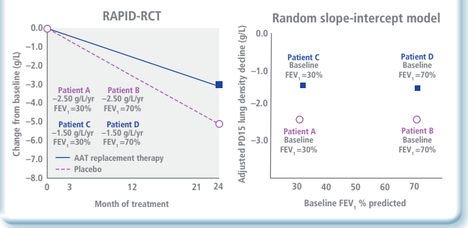
Figure 1: Reduction in annual lung density decline rates (adjusted PD15) at TLC over 24 months (ITT population)



Random slope-intercept model

- A random slope-intercept model was performed with baseline lung function parameters as covariate (FEV_1 % predicted, DL_{CO} and baseline-adjusted PD15)
- In this model the slope and intercept for the change in adjusted PD15 is calculated individually for each patient (**Figure 2**)
- Each symbol on the graph represents one patient and their individual trajectory of lung density decline plotted against their baseline lung function

Figure 2: Random slope-intercept model

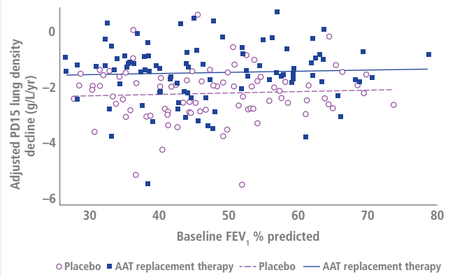


Results

Effect of baseline co-variants on disease progression

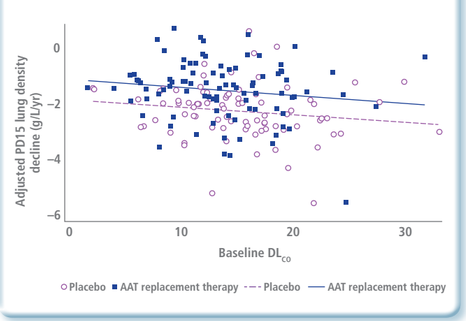
- There was a significant loss of lung density with time (p<0.001)
- Baseline FEV_1 % predicted did not affect changes in annual lung density decline rates (**Figure 3**; p=0.1015)
  - The regression line for the annual lung density decline rate versus baseline FEV_1 % predicted was flat
  - There was no interaction between treatment group and baseline FEV_1 (i.e., both curves were equally flat)
- Active treatment was associated with lung density preservation compared to placebo (p=0.0265)

Figure 3: Rate of decline in adjusted PD15 in relation to baseline FEV_1% predicted



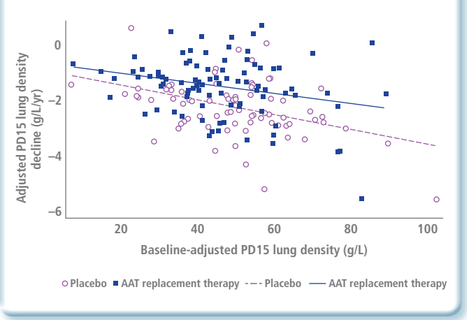
- Similar results were observed when the analysis was replicated with baseline DL_{CO}
- Baseline DL_{CO} did not affect changes in annual lung density decline rates (**Figure 4**; p=0.3280)
- No significant interaction was observed between baseline DL_{CO} and change in PD15
  - The regression lines were parallel
  - The treatment effect was statistically significant (p=0.035)

Figure 4: Rate of decline in adjusted PD15 in relation to baseline DL_{CO}



- Graphically, patients with less emphysema demonstrated a more rapid loss of lung density than more severely affected patients, although this did not reach statistical significance (**Figure 5**)
- The slopes of the regression curves between AAT and placebo were similar (p=0.3912)

Figure 5: Rate of decline in PD15 in relation to baseline-adjusted PD15



Conclusions

- CT lung density is the most sensitive endpoint to assess loss in lung tissue; it was therefore, used in RAPID-RCT to test the effect of AAT treatment versus placebo
- This *post-hoc* analysis confirms the preservation of lung tissue by AAT therapy compared to placebo
- Importantly, the decline in PD15 in relation to conventional pulmonary function parameters seems to be linear across the entire spectrum of patients included in RAPID-RCT
  - Therefore, it can be concluded that treatment with AAT is capable of reducing the loss of lung tissue in both early and late stage emphysema as quantified by pulmonary function measurements
- The use of PD15 as a baseline characteristic showed a more rapid decline in patients with AATD and early lung emphysema, which was significantly reduced by AAT therapy
  - The difference in decline rates between PD15 and FEV_1 % predicted and DL_{CO} in early disease is most likely due to the lack of sensitivity of lung function parameters and a non-linear correlation between loss of alveolar tissue and changes in lung function parameters
- Early treatment of patients with AATD and emphysema may enhance long-term treatment benefit, such as delaying time to terminal respiratory function

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Conflicts of interest

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