PA568

Effect of exacerbations on lung density in Alpha 1 Antitrypsin Deficiency: Subgroup analysis of the RAPID trial programme

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Introduction

- The RAPID trial programme demonstrated that Alpha 1 Antitrypsin (AAT) therapy is effective and disease-modifying in slowing the rate of lung tissue loss in patients with Alpha 1 Antitrypsin Deficiency (AATD), as assessed by computed tomography (CT) lung densitometry[1,2]
- Obtaining accurate CT scans is essential to determine therapy-related changes in lung density
- Theoretically, an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) may temporarily induce changes that could impact lung density
- An increase in lung density could be caused by:
  - Increased amount of sputum
  - Atelectasis
  - Increased inflammation leading to increased amounts of fluid in the interstitium
- A decrease in lung density could be caused by:
  - Increased bronchial obstruction leading to an increase in hyperinflation
- Some clinicians suggest a 6 week exacerbation-free period; however, to date, no clinical study has determined the optimal length of the exacerbation-free period

Aims

- To assess the effect of AECOPD on CT lung density measurements at full inspiration in a *post-hoc* analysis of data from the RAPID trial programme

Methods

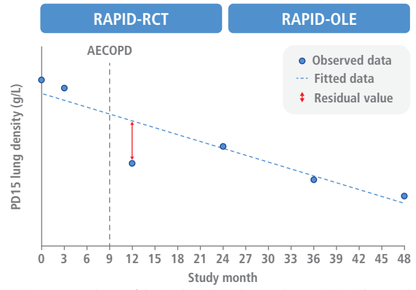
The RAPID trial programme[1,2]

- The 4-year programme consisted of an initial, randomised, double-blind placebo-controlled trial (RAPID-RCT), which evaluated 60 mg/kg/week AAT vs. placebo, and an open-label extension study (RAPID-OLE) in which all patients received active therapy
- Spiral CT scans at total lung capacity (TLC) were performed at baseline and at Months 3, 12, 21, 24, 36 and 48
- Data on AECOPD were derived through a combination of adverse event reporting and diary cards recording symptoms (cough, sputum production and breathlessness), which were collected continuously throughout the study
- Exacerbations were defined according to Anthonisen criteria.

Analysis of associations between exacerbations and lung density

- AECOPD (classified as either non-serious or serious) and adjusted 15th percentile (PD15) lung density at TLC were used for the analysis
- Time (in days) from the nearest lung density assessment to an AECOPD was calculated; the number of days was set to zero if an AECOPD occurred at the time of a lung density assessment
- Raw marginal residuals (i.e., difference between fitted and observed PD15 lung density values) from the primary RAPID trial programme analysis model were calculated for measurements that were closest to a prior AECOPD (**Figure 1**)
  - Residuals from patients with no prior AECOPD were also calculated for comparison; residuals were otherwise grouped into exacerbation occurring ≤2 weeks, ≤4 weeks and ≤6 weeks

Figure 1: Calculation of individual patient raw marginal residuals for PD15 lung density



AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density

Results

- Residual PD15 lung density relative to the time since an AECOPD for all patients in the RAPID trial programme are shown in **Figures 2A** and **2B**
  - The spread of data suggests higher variability (predominantly in a positive direction) in residual values at time points closer to the occurrence of an AECOPD
- Mean residual values associated with non-serious and serious AECOPD were similar at each timepoint (**Figures 3A** and **3B**)
- Mean residual PD15 values were similar for patients with and without prior AECOPD
  - In RAPID-RCT, a trend towards increased mean residual PD15 lung density was seen following an AECOPD that decreased from 2–6 weeks (bold values in **Table 1**); this trend was not validated in RAPID-OLE

Figure 2: Residual PD15 lung density by existence of any prior AECOPD: RAPID-RCT (A); RAPID–OLE (B)

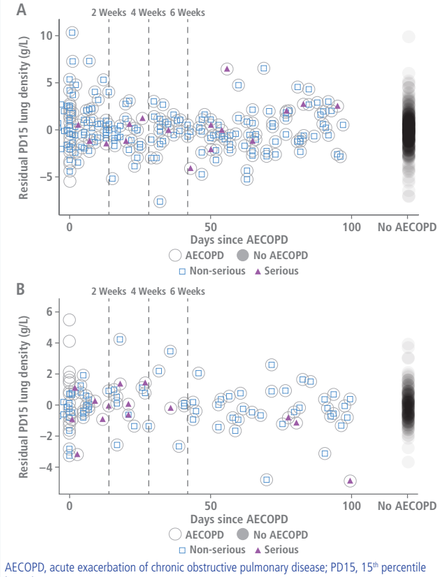


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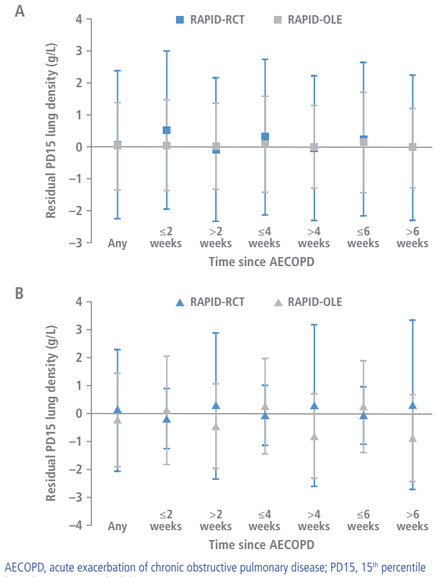
Figure 3: Mean (SD) residual PD15 lung densities for non-serious (A) and serious (B) AECOPD



AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density; SD, standard deviation

Table 1: Mean residual PD15 lung density according to presence/timing of AECOPD

Weeks since prior AECOPD	RAPID-RCT		RAPID-OLE	
	n	Residuals Mean ± SD (g/L)	n	Residuals Mean ± SD (g/L)
Any AECOPD	401	0.06 ± 2.317	203	−0.02 ± 1.405
≤2 weeks	108	**0.46 ± 2.413**	54	0.06 ± 1.510
>2 weeks	293	−0.08 ± 2.267	149	−0.04 ± 1.370
≤4 weeks	132	**0.27 ± 2.356**	68	0.12 ± 1.532
>4 weeks	269	−0.04 ± 2.295	135	−0.08 ± 1.338
≤6 weeks	155	**0.21 ± 2.333**	74	0.15 ± 1.575
>6 weeks	246	−0.02 ± 2.307	129	−0.11 ± 1.294
No AECOPD	384	−0.07 ± 1.900	196	0.02 ± 1.047

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PD15, 15th percentile lung density; SD, standard deviation

Conclusions

- This analysis supports the concept that AECOPD can influence CT lung density measurements
- A 6 week post-exacerbation period showed no untoward influence of AECOPD on CT lung density; this represents a conservative approach to obtain reliable data for clinical trials

References

1. Chapman K *et al. Lancet* 2015;286:360–368
2. McElvaney NG *et al. Lancet Respir Med* 2017;5:51–60

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Conflicts of Interest

CS, NGM, CV and KRC are consultants and grant recipients of CSL Behring. MF, JS, AS and OV are employees of CSL Behring; MW is a consultant to CSL Behring.

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