REPORT OF ECLIPSE AATD *: Evaluation and Control of Lung Inflammation assessed with PET Scanning in Emphysema and Alpha 1-AntiTrypsin Deficiency.*

EudraCT number: 2007-004869
MHRA Ref: 16719/0208/001-002

INTRODUCTION:

ECLIPSE AATD was undertaken as a proof of concept study to explore the potential utility of ^{18}FDG-PET CT as a tool for the quantification and spatial localization of neutrophilic inflammation in the lungs of patients with alpha 1-antitrpysin deficiency and usual COPD and, consequently, a possible *in vivo* method for the assessment of the anti-inflammatory effect of augmentation of alpha 1-antitrypsin to facilitate dose ranging phase 2 studies.

The study comprised of an initial cross-sectional stage in which quantitative ^{18}FDG-PET CT was used to compare the global lung signal in non-smoking subjects with AAT-related emphysema (n=10), against that from non-smoking, non-deficient subjects with emphysema (n=10) and never smoking, normal subjects (n=10). In a second stage, repeat PET CT imaging was performed in the AAT-deficient subjects following 12 weeks of treatment with intravenous Prolastin® at a weekly dose of 60mg/kg. Assessment included assay of biomarkers. Quantitative scintigraphy ('phosphor imaging') of ^{18}FDG uptake from the buffy-coat layer of centrifuged whole blood obtained at the time of ^{18}FDG-PET CT imaging was used to assess the activation of neutrophils in the systemic circulation.

STUDY DESIGN:

Three patient groups were recruited from the ADAPT program and the NHS Respiratory Outpatient clinics at the University Hospitals in Birmingham and Coventry;

1. Normal individuals with FEV_1 greater than 80% predicted FEV_1/VC >70%, and KCO >80% predicted.
2. Patients with pulmonary emphysema (confirmed by previous CT imaging), severe congenital AAT deficiency of phenotype PiZ or other rare null genotypes (not MS, MZ or SZ) and AAT serum level < 11 µM or < 80 mg/dL.
3. Patients (PiMM) with pulmonary emphysema (confirmed by previous CT imaging) due to usual COPD with AAT serum level > 11 µM or >80 mg/dl.

All participants were ≥ 18 years old non smokers or had abstained from smoking for at least 12 months prior to the study and were in the stable clinical state with no respiratory tract infections or acute exacerbations of COPD within the previous 8 weeks. Exclusion criteria were applied according to the study protocol and all subjects gave written informed consent.

Screening at visit 1 included review of diagnostic, historical and eligibility criteria, physical examination, full lung function testing, blood cotinine assay, and pregnancy testing (for patients of child bearing age).

Baseline assessment at visit 2 included health status questionnaire, blood, urine and sputum sampling for biomarkers. Quantitative ^{18}FDG PET CT imaging was performed using an accepted technique [1], as detailed in the study protocol, and additional blood sampling undertaken for ^{18}FDG phosphor imaging.

At visits 3 to 13 (only subjects with AATD) weekly infusions of I.V. Prolastin® were given at a dose of 60mg/kg. Assessment of safety variables and documentation of adverse events, exacerbations and vital signs was performed.
At visit 14, assessment of safety variables and documentation of adverse events, exacerbations and vital signs were performed. Quantitative ^{18}FDG-PET CT imaging was repeated on AATD patients on treatment.

^{18}FDG-PET CT imaging was used to construct a Patlak plot [2] as a surrogate for neutrophilic glycolytic activity throughout the whole lung, as previously described [1] and in accordance with the study protocol. Group comparisons were made using standard statistical tests for comparisons of the mean.

RESULTS:
The study was completed on 30/9/2010.
Patient demographics, expressed as mean (standard error) are shown in Table 1: statistical significance for comparison of the means (Mann-Whitney U test or Fisher's exact test) between the groups is shown.

TABLE 1

				p-value		
	AATD	COPD	Controls	AATD v COPD	AATD v controls	COPD v controls
Age, years	57.2 (2.9)	66.1 (1.8)	59.6 (2.6)	0.052	0.58	0.247
Males, n	9	8	8	1.00	1.00	1.00
FEV1, L	1.7 (0.2)	1.7 (0.3)	3.4 (0.2)	0.912	<0.001	<0.001
FEV1, % predicted	51.5 (5.7)	59.4 (5.4)	112.3 (3.3)	0.280	<0.001	<0.001
FVC, % predicted	114.5 (5.2)	104.6 (3.0)	118.4 (4.3)	0.089	0.497	0.028
FEV_1/FVC ratio	33.9 (3.4)	43.9 (4.1)	75.5 (2.3)	0.052	<0.001	<0.001
TLC, % predicted	116.6 (2.7)	111.1 (3.4)	101.5 (3.7)	0.218	0.006	0.101
Kco, % predicted	60.4 (6.8)	64.9 (7.1)	105.7 (5.9)	0.579	<0.001	0.001
Voxel Index at a threshold of -950 HU, %	24.2 (2.6)	20.2 (2.8)	3.9 (0.4)	0.393	<0.001	<0.001
15^{th} Percentile Point, HU	-973.1 (6.6)	-962.5 (10.9)	-874.0 (5.8)	0.529	<0.001	<0.001

One serious adverse event was reported; a complication of unresolving epistaxis that was considered unlikely to be related to treatment but required admission to the Otorhinolaryngology ward to achieve hemostasis. One patient was withdrawn from the study following the development of a rash after the first infusion of Prolastin.

The results of whole lung Patlak analysis and phosphor imaging, expressed as mean (standard error) with statistical significance for comparison of the means (Mann-Whitney U test) between the groups, are summarized in Table 2:

TABLE 2

					p-value			
	AATD baseline	AATD on treatment	COPD	Controls	AATD baseline v on treatment	AATD v COPD	AATD v controls	COPD v controls
Patlak gradient (ml^{-1})	0.0041 (0.0004)	0.0038 (0.0004)	0.0061 (0.0005)	0.0035 (0.0002)	0.579	0.005	0.315	< 0.001
Phosphor imaging[#]	0.206 (0.030)	0.189 (0.044)	0.144 (0.032)	0.233 (0.074)	0.529	0.133	0.740	0.299

[#] ratio of buffy coat activity : plasma activity.

CONCLUSIONS:

Pulmonary ^{18}FDG uptake is significantly higher in subjects with usual COPD than in subjects with AATD and healthy control subjects, which suggests greater pulmonary neutrophilic glucose uptake in this group. Phosphor imaging data did not identify any differences between the groups that would suggest an increase in uptake of ^{18}FDG by neutrophils within the systemic circulation.

The data do not provide evidence that would indicate a role for ^{18}FDG PET CT as a method for monitoring neutrophilic inflammation in AATD. However, the findings of a previous study by Jones *et al*. [2] are reproduced and provide confirmation that this imaging modality may have a role in usual COPD.

The finding that pulmonary ^{18}FDG uptake is significantly different between subjects with AATD-related emphysema and usual COPD is both unexpected and contrary to current understanding of the pathogenesis of these two conditions. Whilst this may reflect variation in pathogenesis, it is evident that greater understanding of the association between neutrophil glucose transport and metabolism, lung inflammation and the destructive processes that lead to emphysema is required to interpret the differences in ^{18}FDG PET CT signal between these two patient groups. Further regional analysis of the data is also clearly indicated.

REFERENCES:

1. Jones HA, Marino PS, Shakur BH, Morrell NW. *In vivo* assessment of lung inflammatory cell activity in patients with COPD and asthma. *Eur Respir J* 2003;21:567–573.
2. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data: generalizations. *J Cereb Blood Flow Metab* 1985;5:584–590.