molecular mechanisms underlying CS insensitivity are not fully known. Here, we hypothesise that reduction in the expression of the Glucocorticoid receptor (GR) and Importin 7 are related to CS insensitivity. This aims project were to compare the gene expression of GR and Importin 7 between severe asthmatics and mild/moderate asthmatics or healthy controls of the U-BIOPRED cohort. We then investigated whether changes in their expression, correlated with changes in clinical features and expression of other genes.

Methods The U-BIOPRED database contains data on mRNA expression, lung function, medication usage, blood, urine and sputum samples for their subjects (n=611). Using an unbiased approach to analyse the data we will initially used Gene Set Variation Analysis (GSVA) to look for differences in expression of GR and Importin 7 between the severe asthma, mild/moderate asthma and healthy volunteer cohorts. We then characterised the asthmatics into subjects with high (top 25%, compared to healthy controls) or low (bottom 25%) expression of GR or Importin 7 and then compared clinical characteristics and gene expression profiles between the high and low expressing GR or Importin-7 groups.

Results Severe and non-severe asthmatics had reduced GR expression in endobronchial biopsy and brushings samples compared to healthy controls. There were no significant differences in lung function, blood analytes or exacerbation rates between high or low GR expression groups. Severe non-smoking asthmatics had reduced Importin 7 expression in sputum compared to mild/moderate asthmatics and healthy controls. Low Importin 7 group had lower means in FEV1%, FEV1/FVC, higher means in blood and sputum neutrophils%, IL-6 and hCRP.

Conclusions Reduced Importin-7 expression in sputum samples of asthmatics correlated with reduced lung function scores, increased neutrophilic inflammation and more oral CS use.

S65 QUANTIFICATION OF 'WHOLE LUNG' PULMONARY EOSINOPHILIC INFLAMMATION USING RADIOLABELLED AUTOLOGOUS HUMAN EOSINOPHILS

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10.1136/thoraxjnl-2017-210983.71

Background Eosinophils are key mediators of allergic inflammation. The ability to localise and quantify eosinophilic inflammation *in vivo* would facilitate patient endotyping and evaluation of eosinophil-targeted therapeutics. We aimed to quantify eosinophil distribution and organ-specific uptake in healthy subjects, asthmatics, and patients with focal pulmonary eosinophilic inflammation.

Methods We injected autologous radiolabelled eosinophils into 8 healthy volunteers, 15 asthmatics (7 obese and 7 non-obese), and 3 patients with focal eosinophilic inflammation and monitored eosinophil distribution (planar imaging, single photon emission computed tomography – SPECT)/CT). Lung accumulation of technetium-99 m-labelled eosinophils was quantified (Patlak-Rutland analysis). Whole body indium-111-labelled eosinophil distribution and loss were further assessed in 5 healthy volunteers and 7 asthmatics using a whole body counter.

Findings Pulmonary eosinophil clearance was increased in patients with focal eosinophilia (0·0033 ml/min/ml; 95% CI −0·005–0·011; p=0.02) compared to asthmatics (0·0007 ml/min/ml; 95% CI 0·0003–0·0010; p=0.14) and controls (0·0003 ml/min/ml; 95% CI $-7{\cdot}5 \times 10^{-5}$–0·0008). Absolute lung eosinophil migration was elevated in patients with focal inflammation (5932 eosinophils/min/ml; 95% CI −14351–26215, p=0.01) and asthma (364 eosinophils/min/ml; 95% CI 38–689; p=0.03) versus healthy volunteers (38 eosinophils/min/ml; 95% CI −11–87). Stratification of asthmatics based on BMI revealed increased pulmonary eosinophil clearance in obese (0·001 ml/min/ml; 95% CI 0·0007–0·001; p=0.02) versus non-obese asthmatics (0·0003 ml/min/ml; 95% CI −0·0002–0·0009).

Interpretation Eosinophil radiolabelling can quantify pulmonary eosinophilic inflammation, with the potential for patient endotyping and testing eosinophil-targeted treatments.

Funding Medical Research Council, Wellcome Trust, Asthma UK, Cambridge NIHR Biomedical Research Centre.

S66 LONG-TERM AZITHROMYCIN THERAPY IMPROVES CLINICAL OUTCOMES IN AN INFECTIVE PHENOTYPE OF SEVERE ASTHMA

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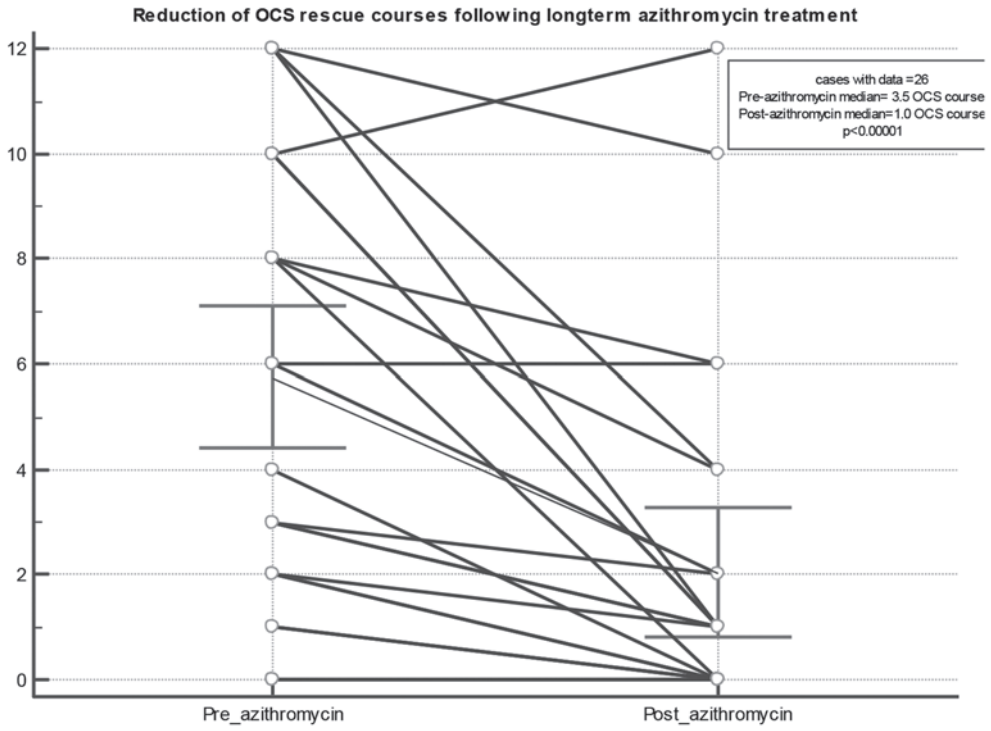
10.1136/thoraxjnl-2017-210983.72

Introduction Azithromycin is a macrolide with antibiotic and anti-inflammatory properties, which may reduce exacerbations and improves clinical outcomes in severe asthma. However, the target population and clinical utility of azithromycin in real life setting remain uncertain.

Aim To determine the efficacy and safety of long-term azithromycin treatment in severe asthma in real life setting.

Methods Patients attended a tertiary severe asthma between 2013 to 2016 were clinically characterised using pre-designed protocol and data were recorded on the dendrite system. The clinical outcomes of patients treated by long-term azithromycin (≥4 months) were compared for the 12 months before and 12 months on treatment using parametric and non-parametric analysis.

Results Out of a total number of 259 patients entered on the registry, 46 (17.7%) patients had long- term azithromycin treatment. The mean age of this group was 50 years. (range 25–72), 33 (66%) females, mean BMI 32±8.4 kg/M^2, 41 (80%) had infective phenotype (≥4 LRTI per annum and/or chronic productive cough), 13 (23%) had CT-scan confirmed bronchiectasis, mean ICS 1620 mcg/day and 13 (26%) were on maintenance OCS. The mean FEV1=1.96 L±0.73,%predicted FEV1=69.4±24.3, mean FEV1/FVC ratio 64.6±16.5, mean FeNO 26±27.2 ppb, mean blood eosinophil 0.3*10^9/l, and mean blood neutrophil was 6.2±2.2*10^9/l. We observed significant reduction in the mean number of OCS requiring exacerbation in the 12 months on treatment compared to the 12 months pre-treatment (figure 1). There was also significant reduction in LRTI frequency from median=4.5 per annum to 1.0 (p<0.00001) and hospital admissions from mean of 1.17 ±2.4 to 0.24±0.7 (p=0.01). Also statistically non-significant improvement in ACQ-7 mean 3.5±1.26 to 3.18±1.3 (p=0.09) and FEV1 1.72 to 1.91 (p=0.36). The treatment was generally well tolerated with 35 (76%) of patients had positive



Abstract S66 Figure 1

response, whilst 11 patients (23.9%) discontinued due to lack of benefit (n=8) or side effects (n=3).

Conclusion Long-term azithromycin therapy improved clinical outcomes in this sub-population of severe asthma of infective phenotype with acceptable safety profile. Further research is warranted to confirm these findings.

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S67 PERSISTENT FREQUENT EXACERBATORS: A SUBTYPE OF SEVERE ASTHMA

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10.1136/thoraxjnl-2017-210983.73

Introduction and Objective Frequent exacerbations (≥2 exacerbations in the past year) is a prognostic factor in severe asthmatics and is associated with increased morbidity and mortality. Using clinical and transcriptomic data, we sought to characterise a clinical subtype of asthma associated with persistent frequent exacerbations (PFE) which is defined by frequent exacerbations for minimum 2 consecutive years.

Methods Baseline and longitudinal clinical and transcriptomic data from 311 severe asthmatics from the U-BIOPRED study was analysed to find distinct clinical characteristics of the PFE group. The longitudinal data was collected 12–18 months after the baseline visit. We also sought to annotate the PFE group with gene set variation analysis (GSVA) using gene signatures associated with active viral infection and immune response.

Results Out of 311 patients, 193 were frequent exacerbators (FE) at baseline. 109 (56.5%) of FE subjects at baseline remained FE at the longitudinal follow-up and were designated PFE. This group of patients had earlier-onset of asthma (25 [28] yrs vs 28 [33] yrs, median [interquartile range]), higher BMI (30.3±6.8 vs 28.4±5.3 kg/m^2, mean ±SD) and higher eczema diagnosis (37.61% vs 28.22%) compared with infrequent and non-persistent exacerbators. However, they had lower atopy positive blood tests(57.80 vs 68.32%). These patients also had poor lung function and lower airway conductance with a lower mean Sgaw (0.72±0.6 vs 0.99±0.8, mean ±SD). The number of subjects taking oral corticosteroids (60.2 vs 37.6%) and xanthines (34.3 vs 12.6%) was greater in the PFE group. PFE patients were more poorly controlled (ACQ; 2.7±1.2 vs 2.0±1.1, mean ±SD) and had a worse quality of life (AQLQ; 4.2±1.1 vs 4.6±1.3, mean ±SD) with higher anxiety and depression (HADS; 14.0 ±7.9 vs 12.1±8.2, mean ±SD). GSVA analysis identified gene signatures associated with an active viral response to be differentially enriched amongst the PFE in nasal brushing samples.

Conclusion This study identified a group of asthmatics, defined by PFE who have poorly managed and difficult-to-treat asthma. It also identified a potential role of the minimally invasive nasal brushing sample to identify PFE and thus allow for early intervention and improvement in the morbidity and mortality in this group of patients.