S91 FUNGAL SENSITISATION AND BRONCHIECTASIS IN A SEVERE ASTHMA CLINIC

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Aims Allergic bronchopulmonary aspergillosis (ABPA) and Severe asthma with fungal sensitivity (SAFS) are well recognised in the severe asthma population. Sensitisation to other moulds has also been described. Defined radiological, immunological, and physiological features are associated with these conditions. We describe these features within a severe asthma population, identifying radiological airway abnormality and the association with fungal sensitisation, airway obstruction and immunological markers.

Methods Retrospective database analysis of referrals to a severe/difficult asthma service with comparison of radiological, immunological and physiological features in patients with severe refractory asthma (SRA), with and without fungal sensitivity (FS).

Results (table1) 141 patients with SRA, defined according to ATS criteria, were identified. 67 patients (47.5%) had an abnormal CT scan; the most common abnormalities being bronchial wall thickening (38.8%), bronchiectasis (28.3%) and mucus plugging (2.9%). 35 patients (24.8%) demonstrated fungal sensitisation (FS), 30 to *Aspergillus fumigatus* and 5 to "mould mix". All patients, regardless of fungal sensitivity (FS) demonstrated a strongly eosinophilic phenotype with IgE, ENO and blood eosinophil levels of 1450.03 kU/L, 47.36 ppb and 0.95 x10⁹ for those with FS and 387.88 kU/L, 59.96 ppb and 0.8x10⁹L, for those without FS. Consistent with a diagnosis of SRA obstructive spirometry was seen across both groups with post bronchodilator FEV1:FVC ratios of 0.57 (FS) vs 0.62 (SRA) CT appearances most commonly associated with fungal sensitisation were bronchial wall thickening (22.9%) and bronchiectasis (34.3%). In the presence of bronchiectasis and fungal sensitisation equal incidence of proximal and distal disease distribution was observed. Division of those with fungal sensitivity into ABPA, allergic bronchopulmonary mycosis (ABPM), defined according to criteria by Agrawal *et al*, SAFS and severe asthma without fungal

sensitisation also demonstrated further differences (figure 1). Bronchiectasis was seen most frequently in those with SAFS and of the patients with ABPA and ABPM all patients had a serological diagnosis apart from 2 where peripheral bronchiectasis was demonstrated.

Conclusions In this population SRA is characterised by a strongly positive eosinophilic phenotype, airflow obstruction and a high prevalence of radiological abnormality regardless of FS. FS is associated with bronchiectasis even when diagnostic criteria for ABPA are not met.

S92 NEBULISED AMPHOTERICIN IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA) AND SEVERE ASTHMA WITH FUNGAL SENSITISATION (SAFS)

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Background and Rationale Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) are debilitating lung diseases whose treatment is not yet fully established. Some published case series suggest that nebulised amphotericin may have a role in the treatment of cystic fibrosis ABPA but little is known regarding its appropriateness in asthmatic ABPA and SAFS patients. We assessed the efficacy and safety of nebulised Amphotericin as second and third line therapy.

Methods 20 adult asthmatics with SAFS (n = 11) and ABPA (n = 9) were treated with nebulised amphotericin (January 2011- May 2013). All patients had either failed itraconazole (n = 8), voriconazole (n = 5) or developed adverse events (AEs) to either agent (n = 7). 10mg of Nebulised amphotericin B (Fungisone) was administered using a nebulizer twice/day. We audited clinical, radiological and immunological response, including change in the Asthma Quality of Life Questionnaire (AQLQ-J) scores. We also examined Asthma Control Questionnaire (ACQ) scores, change in lung function (FEV1), change in IgE (total and specific) and healthcare utilisation. Patients were followed up for 12 months.

Abstract S91 Table 1.

	ABPA (n=12) 1 bronchiectasis, 11 seropositive	ABPM (n=5) 1 bronchiectasis, 4 seropositive	SAFS (n=18)	SRA no FS (n=106)
Female	8 (67%)	3 (60%)	12 (67%)	63 (59%)
Age at Diagnosis yrs	9.3	8.4	17	23.6
Asthma duration yrs	30	23.6	42	26.5
FEV1	64.7%	73.4%	56.5%	67.2%
FEV1 / FVC	62	64	53	62
Residual Volume (% predicted)	180	139	163	135
KCO (% predicted)	96%	86%	86%	97%
IgE kU/L	2664	2402	378	389
FeNO ppb	44.7	54	47	60
Blood EØ x10 ⁹ /L	0.93	0.68	1.03	0.8
Oral prednisolone mg/d	3.75	6.0	5.0	6.2
LTOS therapy	9 (75%)	1 (20%)	10 (56%)	47 (44%)
Bronchiectasis	1 (8%)	1 (20%)	10 (56%)	6 (6%)

Results There were 20 patients analysed (SAFS, $n = 11$) and (ABPA $n = 9$), M: F = 8:12, median age 65.5 yrs (range = 24–78). The median duration of therapy was 30 days (IQR, 0.0–142). Clinical benefit was observed in 2 (10%) in which mean ACQ score improved from 6 to 2, overall mean AQLQ score improved by 0.95 and mean FEV1 improved by 1.2 L (63.1%). Seven (35%) failed the challenge due to bronchospasm. 11 (55%) discontinued within 12 months of therapy due to delayed bronchospasm ($n = 3$, within 4 weeks), equipment problems ($n = 4$) and lack of clinical benefit ($n = 4$) (fig 1). There were no significant changes in immunological and radiological outcomes.

Conclusion Our data suggests that the overall efficacy of nebulised amphotericin in this group of patients may be poor and is associated with high frequency of adverse events. However, the responses were excellent in 2 (10%) patients. It is not clear which patients are likely to respond. Further studies need to be conducted to establish the optimal dose range (dose, frequency), nebulizer type, pressures and identification of patients who may respond.

Abstract S92 Figure 1. Reason for treatment failure in patients treated with non-liposomal, nebulised Amphotericin B (Fungisone). Na = Not applicable (ie no failure observed).

S93 LARYNGEAL OBSTRUCTION DURING EXERCISE IS PREVALENT IN SEVERE ASTHMA

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Introduction Reduced exercise capacity is a common problem for patients with severe asthma, yet the reason for this remains unclear. Exercise induced laryngeal obstruction (EILO) is now recognised to cause dyspnoea on exertion but has never been studied in patients with severe asthma. We therefore undertook this study, utilising a gold standard endoscopic visualisation technique, to evaluate laryngeal function during exercise, in a well-characterised cohort of patients with severe asthma.

Methods Adult patients with severe asthma were recruited following a systematic assessment of their disease. All subjects reported impairment of activities of daily living despite treatment. Subjects underwent a symptom-limited continuous

laryngoscopy during exercise (CLE) test. Laryngeal function / EILO was graded against a validated score. Measures of asthma control, perceived dyspnoea, lung function and procedure tolerability were recorded.

Results 32 patients ($n = 25$; female) completed CLE evaluation (Table 1). All patients were prescribed step 4/5 BTS treatment; 75% were prescribed maintenance oral corticosteroid. Despite this, patients reported poor disease control and high perceived dyspnoea (Table 1). EILO of at least moderate severity (graded ≥ 2 from max 3) was evident in 14 (44%) patients. The pattern and respiratory phase of EILO varied; inspiratory phase predominant ($n = 7$; 22%), expiratory phase predominant ($n = 5$, 16%), present in both phases ($n = 2$). Subjects with expiratory predominant EILO were more likely to have obstruction at the glottic level (i.e. vocal cord abduction) and poorer lung function. The CLE test was well tolerated; majority of subjects reported no/minimal procedural discomfort.

Conclusion Exercise induced laryngeal obstruction is highly prevalent in patients with severe asthma and is associated with dyspnoea. This abnormal laryngeal function was not evident at rest and may impair physical exercise capacity. Further work is required to explore underlying mechanisms and relationships with dyspnoea during activities of daily living.

Abstract S93 Table 1. Subject characteristics.

	All ($n = 32$)	Expiratory EILO ($n = 5$)	Inspiratory EILO ($n = 7$)
Age (yr)	43 (12)	47 (11)	39 (15)
BMI (kg/m^2)	29.8 (6.4)	27.1 (4.1)	29.1 (7.8)
FEV ₁ (% predicted)	68 (18)	47 (18)	74 (17)*
FEV ₁ /FVC	0.63 (0.14)	0.52 (0.17)	0.70 (0.14)
Asthma Control test (x/25)*	12 (6–23)	12 (7–20)	9 (6–15)
Nijmegen Score (x/64)*	23 (6–45)	23 (10–45)	25 (12–45)

Data presented as Mean (SD) or Median (range).

* $P < 0.05$ difference between subgroups

Mechanisms of lung injury

S94 TUMOUR NECROSIS FACTOR RECEPTOR 1 INHIBITION USING A NOVEL INHALED HUMAN ANTIBODY REDUCES INFLAMMATION IN A HUMAN MODEL OF LUNG INJURY INDUCED BY INHALED LIPOPOLYSACCHARIDE; A RANDOMISED PLACEBO-CONTROLLED CLINICAL TRIAL

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Introduction and Objectives Tumour Necrosis Factor receptor 1 (TNFR1) transduces the pro-inflammatory activity of TNF- α , whereas signalling through TNFR2 may contribute to tissue repair. Attenuation of TNFR1 signalling, whilst simultaneously preserving the effects of TNFR2 signalling, may be beneficial in management of acute lung injury (ALI). GSK1995057 is a novel, fully human antibody fragment (domain antibody) that selectively binds TNFR1 and antagonises signalling of TNF- α via TNFR1.