S78 DIFFERENTIATION OF MONOCYTES TO PRO-INFLAMMATORY FORMS IS INFLUENCED BY CIGARETTE SMOKE AND HLA TYPE IN COPD

doi:10.1136/thoraxjnl-2011-201054b.78

P R Newby, C Schmutz, C R Buckley, R A Stockley, A M Wood. *University of Birmingham, Birmingham, UK*

Background There are many genetic influences documented on both lung function and susceptibility to COPD. In GWAS of pulmonary function several hits in the region of the MHC on chromosome 6 have been found, and we have shown previously that HLADR3 positive individuals have lower FEV_1 than those without this HLA type. This is an HLA type classically associated with autoimmunity. Interactions between HLA type and cigarette smoke are recognised in autoimmune diseases.
Hypothesis HLA type influences differentiation of monocytes in the presence of cigarette smoke.
Methods 15 ex and never smokers with COPD and 5 healthy controls were studied. PBMCs were isolated and exposed to varying concentrations of cigarette smoke extract (CSE) for 90 min. CD14 and CD16 markers were used in flow cytometry to ascertain relative expression and absolute cell counts for each monocyte subpopulation, defined as CD14++CD16- (classical), CD14++CD16+ (anti-inflammatory) and CD14+CD16++ (non-classical). Within the patient group differences in baseline profile and response to CSE were compared between ex-smokers and those that had never smoked. Patients were HLA class II typed as described previously[1] and the same comparisons made between DR3 positive and negative patients.
Results At baseline the MFI for CD14 was lower in COPD than health (p=0.04), although no clear differences in cell counts were seen. Counts were generally higher in ex-smokers, although no clear differences in subpopulations were seen. On exposure to cigarette smoke there was a dose dependent rise in classical monocytes, which was more marked in DR3+ patients and never smokers.
Conclusions CSE induces a pro-inflammatory phenotype of monocytes, and this occurs most in HLADR3+ individuals. This could be the mechanism behind lower FEV_1 in DR3+ individuals.

REFERENCE

1. **Bunce M,** *et al*. *Tissue antigens*. 1995;**46**:355–67.

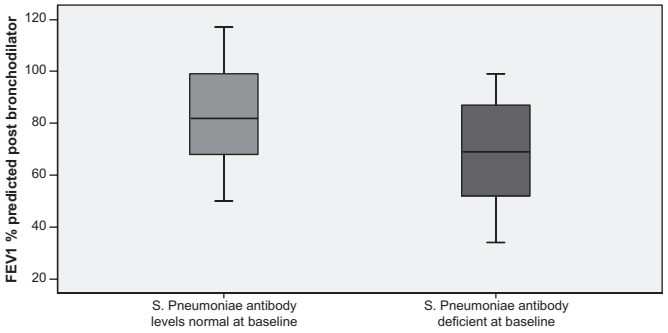
Severe asthma in children and adults

S79 SPECIFIC FUNCTIONAL ANTIBODY DEFICIENCY IS ASSOCIATED WITH A REDUCTION LUNG FUNCTION IN THE SEVERE ASTHMA POPULATION

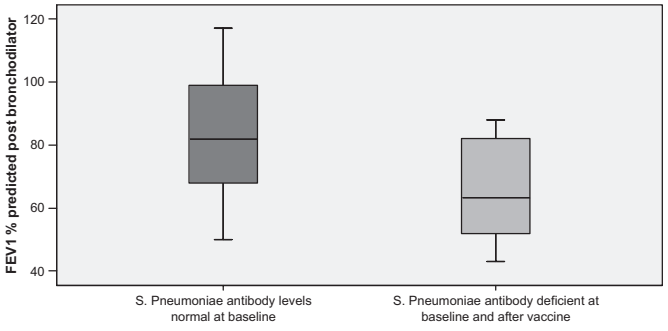
doi:10.1136/thoraxjnl-2011-201054b.79

H Wardman, R Niven, G McCumesky, L J Holmes, D Menzies, G Tavernier. *University Hospital of South Manchester, Manchester, UK*

Background *Haemophilus influenzae type B (Hib)* and *Streptoccus pneumoniae* are leading causes of LRTI in the severe asthma population. Patients attending our regional severe asthma service have functional antibody levels tested against these two bacteria. Those with weakened immune systems may go on to require immunoglobulin therapy. The prevalence and impact of specific antibody deficiency within the severe asthma population has yet to be established.
Objective We sought to quantify the number of patients who are deficient in antibodies against *Hib* and *S pneumoniae* within the severe asthma population, both at initial assessment and after vaccination.
Methods Data from our regional clinic stored on a National Severe Asthma database was supplemented with information from the UHSM clinical results database, which contains blood antibody levels against *Hib* and *S pneumoniae* and lung physiology. Deficiency in *Hib* was defined as antibody levels of <0.15 μg/ml and for *S pneumoniae*, 6 out of 12 strains tested measuring >0.35 μg/ml. Only patients assessed after January 2008 were included. The prevalence of radiological abnormality, *Aspergillus* sensitisation, blood and sputum eosinophil counts, and lung function between severe asthma patients with antibody deficiency, and those with normal antibody levels were then compared.
Results Among the patients tested for immunity to *S pneumoniae* (n=94) and *Hib* (n=97), 33% and 51% respectively were found to be deficient at initial assessment. In patients with baseline immune deficiency, 70% of those that received the Pneumovax vaccine had persistently low antibody levels against *S pneumoniae*, (p=0.03), and 20% who received Menitorix remained deficient in *Hib* antibodies. The mean post bronchodilator FEV_1 for patients with normal *S pneumoniae* antibody levels was 82.4% predicted compared to 68.8% predicted in those who were deficient at initial assessment (p=0.018), and 65.3% predicted in patients with persistently low antibody levels even after vaccination (p=0.049). All other variables showed no difference between the groups.



Abstract S79 Figure 1



Abstract S79 Figure 2

Conclusion This study demonstrates for the first time that antibody deficiency to *S pneumoniae* and *Hib* is common in patients with severe asthma, can persist despite vaccination in a significant proportion of individuals and is associated with worse lung function.

S80 LOCALISATION OF THE SITE OF FIXED AIRFLOW OBSTRUCTION IN MODERATE TO SEVERE ASTHMA USING HYPERPOLARISED HELIUM-3 MRI

doi:10.1136/thoraxjnl-2011-201054b.80

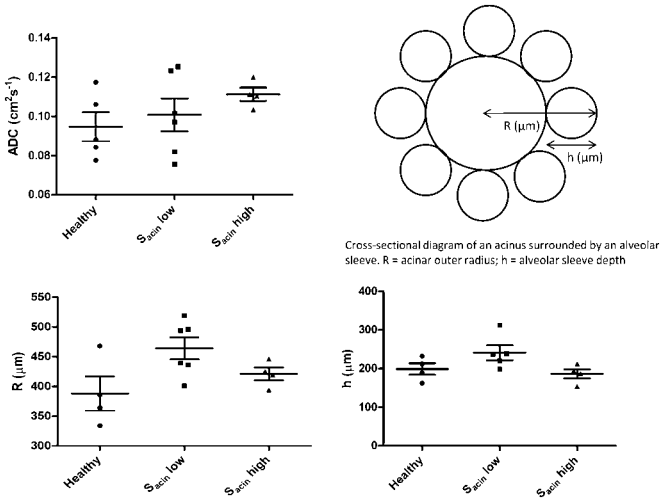
[1]S Gonem, [2]I Ball, [1]S Corkill, [1]D Desai, [1]A Singapuri, [3]P Gustafsson, [2]J Owers-Bradley, [1]C Brightling, [1]S Siddiqui. *[1]Glenfield Hospital, Leicester, UK; [2]University of Nottingham, Nottingham, UK; [3]Queen Silvia Children's Hospital, Göteborg, Sweden*

Introduction and Objectives Moderate and severe asthma are often associated with a degree of fixed airflow obstruction. We aimed to

comprehensively characterise a group of patients with moderate to severe asthma using a variety of standard and novel physiological techniques, including hyperpolarised helium-3 magnetic resonance imaging (He-3 MRI), in order to non-invasively localise the major site of airway obstruction within the bronchial tree.

Methods We recruited 17 patients with moderate asthma (GINA 3/4), 12 patients with severe asthma (GINA 5) and fifteen healthy control subjects. Participants undertook standard pulmonary function tests, multiple breath washout (MBW) and impulse oscillometry (IOS). Five healthy subjects and 10 patients with asthma also undertook He-3 MRI. Two MRI sequences were performed. The first sequence allowed derivation of the apparent diffusion coefficient (ADC), a measure of alveolar airspace size, while the second sequence allowed derivation of the modelled parameters R and h, representing acinar outer airway radius and alveolar sleeve width respectively, as introduced by Yablonskiy *et al*.[1]

Results Patients with asthma displayed evidence of fixed airflow obstruction and air trapping, with reduced FEV_1 and increased RV/TLC ratio, compared to healthy controls. However, Kco was higher in patients with asthma than in controls. The MBW small airway marker S_{acin} was significantly raised in patients with asthma compared to healthy controls (healthy=0.126, GINA 3/4 asthma=0.173, GINA 5 asthma=0.213; p=0.03), confirming the presence of acinar airspace disease in patients with moderate and severe asthma. S_{cond}, a conductive airway marker, did not differ significantly between the groups. ADC, R and h also did not differ significantly between healthy controls and patients with asthma, or between asthmatic patients with and without evidence of acinar airspace disease (*see* Abstract S80 figure 1), suggesting that the alveoli are not a major site of involvement in asthma.



Abstract S80 Figure 1 Characterisation of asthma patients with and without acinar disease by He-3 MRI. Means and standard errors of the mean are displayed. Data were analysed using one-way analysis of variance with no statistically significant differences found between groups.

Conclusion Our results suggest that the site of fixed airflow obstruction in patients with moderate to severe asthma may be localised to the proximal acinus, and that the alveoli are relatively spared.

REFERENCE

1. **Yablonskiy,** *et al*. *J Appl Physiol* 2009;**107**:1258–65.

S81 REFRACTORY ASTHMA IN THE UK: A FOLLOW-UP ANALYSIS

doi:10.1136/thoraxjnl-2011-201054b.81

[1]J Sweeney, [2]C E Brightling, [3]A Menzies-Gow, [4]R M Niven, [1]L G Heaney. *[1]Centre for Infection and Immunity, Queen's University, Belfast, UK; [2]Institute for Lung Health, University of Leicester, Leicester, UK; [3]NIHR Respiratory Disease, Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London, UK; [4]North West Lung Centre, University of Manchester, Manchester, UK*

Introduction Refractory asthma poses a major healthcare problem with limited therapies currently available and new therapies needed. The British Thoracic Society (BTS) Difficult Asthma Network has previously published demographic data on a cohort of patients with well-characterised refractory asthma[1] using a National Registry and detailed follow-up data is now available.

Methods Data on 349 of the original 382 patients was available from 4 specialist centres across the UK—Royal Brompton Hospital, London, Glenfield Hospital, Leicester, University Hospital of South Manchester and Belfast City Hospital. Data have been used to examine healthcare utilisation, therapeutic strategies and lung function compared to baseline.

Results The median follow-up period was 3.1 years (IQR 1.9—5.5 years). Improvements from baseline were noted in Pre bronchodilator FEV_1% predicted (66%±23.6% vs 72.7%±26.8%; p<0.001) and Pre bronchodilator FVC% predicted (82.7%±20.3% vs 86.5%±21.5%; p<0.01). Reduced rescue steroids (Median 2{IQR 4—6} vs 0 {IQR 2—4}; p<0.001), a reduction in hospital admissions (Median 0 {IQR 0—2} vs 0 {IQR 0—1}; p<0.01) and reduced unscheduled visits to GP's or A&E (Median 4 {IQR 2—6} vs 2 {IQR 0—6}; p<0.05) was seen. The most frequent therapeutic intervention was the introduction of maintenance oral steroids (OCS): 42% of the original cohort was on maintenance OCS at baseline, with 58% on maintenance OCS at follow-up. Most on OCS at baseline remained on OCS but 30 (9%) discontinued and 78 (22%) had OCS initiated. Steroid sparing agents (methotrexate, cyclosporine, azathioprine etc) were tried but showed minimal steroid sparing benefit with a success rate of between 0.6 and 3.2%. Omalizumab was only suitable for trial in 59 (17%) subjects with a response rate of 66%. In those who had a successful Omalizamub trial, 23 (92%; p<0.001) were successful in achieving either a reduction in OCS or complete withdrawal.

Conclusion In specialist centres, healthcare outcomes and lung function are improved in patients with refractory asthma. The most frequent intervention is the progression to maintenance OCS and treatment options remain limited. Steroid sparing agents show little benefit with the exception of Omalizamub.

REFERENCE

1. **Heaney LG,** Brightling CE, Menzies-Gow A, *et al*. Refractory asthma in the UK: cross sectional findings from a UK multicentre registry. *Thorax* 2010;**65**:787—94.

S82 FUNGAL SENSITISATION IN CHILDREN WITH SEVERE THERAPY RESISTANT ASTHMA

doi:10.1136/thoraxjnl-2011-201054b.82

[1]S Castanhinha, [2]A Gupta, [3]M Maglione, [4]S Koo, [5]C Bossley, [5]L Fleming, [2]A Bush, [2]S Saglani. *[1]Department of Paediatrics, Hospital Santa Maria, Universidade de Lisboa, Lisbon, Portugal; [2]Department of Respiratory Medicine, Royal Brompton and Harefield NHS Trust, National Heart and Lung Institute, Imperial College, London, UK; [3]Department of Paediatrics, Federico II University, Naples, Italy; [4]Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong, China; [5]Department of Respiratory Medicine, Royal Brompton and Harefield NHS Trust, London, UK*

Introduction Severe asthma with fungal sensitisation (SAFS) in adults is associated with reduced lung function and increased morbidity [*EurRespir J* 2006;**27**:615—26, *Am J RespirCare Med* 2009; **179**:11—18]. We hypothesised that fungal sensitisation in children with severe, therapy-resistant asthma (STRA) is associated with increased symptoms, medication use and airway inflammation, and reduced lung function.

Methods STRA was defined as before [*Lancet* 2010;**376**:814—25]. All children had been through a detailed assessment to optimise