S10 ARE WE OVERLOOKING PERSISTENT SMALL AIRWAYS DYSFUNCTION IN COMMUNITY-MANAGED ASTHMA?

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[1]WJ Anderson, [2]E Zajda, [1]BJ Lipworth. [1]*University of Dundee, Dundee, United Kingdom;* [2]*University of Abertay, Dundee, United Kingdom*

Background It is unknown if small airways dysfunction persists in asthmatics receiving standard community treatment. Impulse oscillometry (IOS) is a sensitive measure of small airways function. We wished to assess the degree of small airways dysfunction in a cross-section of community-managed asthmatics.

Methods We analysed primary care referral data from persistent asthmatics (n=378) receiving standard community therapy, screened using spirometry and IOS. We compared patients by British Thoracic Society asthma treatment step (2–4).

Results Step 2 were not different from step 3 patients receiving long-acting beta-agonist (LABA). Step 4 patients differed from step 2 by: higher inhaled corticosteroid (ICS) dose ($p<0.0001$); lower forced expiratory volume in 1s (FEV1%, $p=0.02$) and forced mid-expiratory flow (FEF25–75%, $p=0.001$); higher frequency of resonance (Fres, $p=0.02$) and peripheral airway resistance (R5-R20, $p=0.006$); while for steps 3 vs. 4, there were differences in Fres ($p<0.05$) and R5-R20 ($p=0.006$). There were high proportions of abnormality for R5-R20 (>0.03kPa/L/s) at steps 2, 3 & 4 respectively: 64.6%, 63.5% and 69.9%. Step 2 patients receiving extra-fine particle ICS demonstrated lower total airway resistance at 5Hz (R5) versus patients receiving standard ICS (124.1% vs. 138.3%, $p<0.05$), with no difference in FEV1 (Table 1). At step 4, R5 remained elevated at 141.3% despite concomitant LABA, with only 2.4% using extra-fine ICS.

Conclusion There is persistent small airways dysfunction despite treatment at steps 2–4 of current asthma guidelines. Extra-fine ICS may reduce airway resistance at step 2. Prospective studies with extra-fine ICS±LABA at steps 2–4 are required to discern whether improving small airways function might result in long-term improved control.

Abstract S10 Table 1

Variable	Extra-fine ICS (n=67)	Standard ICS (n=125)	p-value
ICS dose (μg/day)	279 (249, 309)	406 (364, 447)	**<0.0001**
FEV_1 (% predicted)	88.9 (84.8, 92.9)	90.3 (87.5, 93.1)	0.56
$FEF_{25–75}$ (% predicted)	63.7 (57.5, 69.8)	67.1 (62.7, 71.5)	0.38
R5* (% predicted)	124.1 (113.5, 135.8)	138.3 (130.0, 147.0)	**<0.05**
R20* (% predicted)	126.0 (117.0, 135.8)	136.7 (130.0, 143.9)	0.07
R5-R20* (kPa/L/s)	0.069 (0.05, 0.088)	0.088 (0.071, 0.105)	0.18
F_{res}* (kPa/L/s)	13.9 (12.6, 15.2)	14.6 (13.6, 15.7)	0.36
FeNO* (ppb)	31.4 (24.9, 39.5)	25.3 (21.9, 29.2)	0.11

Comparisons of extra-fine particle solution formulation of inhaled corticosteroid (ICS) vs. standard particle size (suspension CFC/HFA, or dry powder formulation) ICS outcomes at step 2. Data presented as arithmetic means (95% CI) unless stated. *Geometric mean (95% CI). Means comparison performed using Student's T-test for independent samples (two-tailed), significance $p<0.05$. ICS dose=nominal inhaled corticosteroid dose. FEV_1=forced expiratory volume in 1s. $FEF_{25–75}$=forced expiratory flow between 25–75% of vital capacity. R5=total airway resistance at 5Hz. R20=central airway resistance at 20Hz. F_{res}=frequency of resonance. R5–R20=peripheral airways resistance between 5Hz and 20Hz. FeNO=fractional exhaled nitric oxide.

S11 EXPRESSION OF TENASCIN-C REGULATES AIRWAY SMOOTH MUSCLE DERIVED MATRIX METALLOPROTEINASE-1 IN ASTHMA

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NK Rogers, D Clements, TW Harrison, D Shaw, SR Johnson. *University of Nottingham, Nottingham, UK*

Background Collagenases are differentially regulated in conditions of lung remodelling. Literature documents the capacity of extracellular matrix (ECM) proteins to induce collagenase expression. The current study aims to characterise ECM regulation of the collagenase matrix metalloproteinase-1 (MMP-1) in human airway smooth muscle (ASM) cells, and the applicability of this mechanism to remodelling.

Methods ASM cells were derived from patients with and without asthma and cultured with ECM proteins for 24 hours. MMP-1 gene expression was quantitated by Real-time PCR, with secreted protein and activity levels assessed by ELISA, Western Blotting and fluorometric activity assay. Pathways mediating MMP-1 induction were mapped using a phosphoprotein array, specific inhibitors and blocking antibodies. Tenascin-C and MMP-1 expression were studied in endobronchial biopsies from patients with and without asthma by immunohistochemistry.

Results Tenascin–C increased MMP-1 mRNA, protein and activity in a dose and time dependent manner. Tenascin-C phosphorylated MAPK intermediates ERK and P38, and inhibitors to these intermediates attenuated MMP-1 induction. Blocking antibodies showed this response was mediated by the β1 and β3 integrins. Control tissue showed minimal tenascin-C and MMP-1 expression, but strong co-localising Tenascin-C and MMP-1 expression in the subepithelial layer and to a lesser extent in ASM bundles. ASM cells from patients with asthma had elevated basal levels of MMP-1, which was further increased by Tenascin-C stimulation.

Discussion Tenascin-C upregulates expression and activity of MMP-1 via the β1 and β3 integrin subunits and MAPK signalling in ASM cells. These proteins were increased in lung remodelling diseases, with overlapping localisation. The functional consequences of this observation needs to be evaluated in vivo, however, this could potentially yield a new target for therapeutic in airway remodelling.

Pleural disease

S12 EXPERIENCE WITH INTRAPLEURAL TISSUE PLASMINOGEN ACTIVATOR AND DNASE IN THE TREATMENT OF PLEURAL INFECTION

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[1,2]NI Pitman, [3]RA McCartney, [2]C O'Dowd, [3]KG Blyth, [4]B Choo-Kang, [1]MK Johnson.[1]*Gartnavel General Hospital, Glasgow, UK;* [2]*Victoria Infirmary, Glasgow, UK;* [3]*Southern General Hospital, Glasgow, UK;* [4]*Glasgow Royal Infirmary, Glasgow, UK.*

Introduction Intrapleural infection remains a significant cause of morbidity and mortality. In many patients medical management with chest tube drainage and antibiotics fails and surgical intervention is required. The MIST2 trial reported improved resolution following intrapleural treatment with combined tissue plasminogen activator and DNase (tPA/DNase).

Aims To study the outcomes in patients with pleural infection treated with tPA/DNase over a one year period in a 1,109 bed city centre hospital.

Methods A prospective audit was undertaken of all patients with pleural infection treated with intrapleural tPA/DNase. The decision to initiate therapy was at the discretion of the treating team. The main outcomes were changes in chest drain output and CXR opacification, complications, and surgical intervention. The area of pleural opacity was calculated using the method described by the MIST2 group.

Results Ten patients were treated over a one year period, all of whom had clinical features of infection and yielded frank pus or pleural fluid with a pH below 7.2.

Treatment with tPA/DNase was not initiated as a first line therapy in any patient. All were initially managed with chest tube drainage and antibiotics and the decision to initiate tPA/DNase was due to subsequent poor or absent drain output combined with evidence of persistent pleural fluid.

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