S66 IS HOSPITAL READMISSION AN APPROPRIATE OUTCOME MEASURE FOR COMMUNITY-ACQUIRED PNEUMONIA?

doi:10.1136/thoraxjnl-2011-201054b.66

J Brettell, M A Woodhead. *Manchester Royal Infirmary, Manchester, UK*

Introduction and Objectives There is no ideal outcome measure for studies in community-acquired pneumonia (CAP). Readmission to hospital within 30 days is one proposed measure which coincidentally the NHS now imposes financial penalties on Trusts for. We sought to investigate the frequency and validity of this measure for CAP and to examine factors predictive of readmission in CAP.

Methods All adult cases (ICD10 J10–J18) admitted in 2010 were identified from Trust Information records. Those readmitted within 30 days of discharge were regarded as cases and reason for readmission was ascertained. The two consecutive admissions after each readmission case were used as controls to identify features predictive of readmission. All were validated as CAP by inspection of radiographs and case records.

Results 562 cases were identified. 93 were excluded. 96 (20%) of the remaining 469 died. 55 (12%) were readmitted. Eight of these were excluded and six case notes were lost leaving 41 cases who were compared with 72 controls who had not been readmitted. Of these 113, mean age was 61 (95% CIs 57–65), 59% were male, 85% had one or more comorbid disease, 83% were admitted from their own home, 54% were CURB65 0–1, 26% CURB65 2, 23% CURB65 3–5. Readmission was considered by the admitting physician to be CAP-related in only 16 (39%), but even in these CRP was raised at readmission in only 81%. Non-CAP reasons for readmission were varied and were distributed across at least 8 disease areas. Only 13 (32%) of all readmissions were considered to have been preventable at the first admission. Age (OR 0.995; 95%CI 0.959 to 1.033), presence of comorbid disease (2.045; 0.415 to 10.089), Charlson comorbidity index (1.082; 0.785 to 1.491), initial length of stay (1.009; 0.984 to 1.034), CURB65>0 (2.003; 0.551 to 7.282) and initial treatment with tazocin (2.502; 0.804 to 7.784) were significantly related to readmission, but CIs all included unity.

Conclusion The low frequency, lack of relationship to CAP in the majority and lack of preventability at the index admission suggest that readmission within 30 days of discharge is not a valid outcome marker for CAP. Age and markers of biological unfitness predict readmission.

Linking mechanisms to prognosis in pulmonary arterial hypertension

S67 CHARACTERISATION OF THE ENDOTHELIAL OUTGROWTH CELL

doi:10.1136/thoraxjnl-2011-201054b.67

M Toshner, M L Ormiston, B Dunmore, J Waters, E McKinney, A Rana, N Morrell. *University of Cambridge, Cambridge, UK*

The existence of cells circulating in the peripheral blood with the capacity of an endothelial progenitor cell (EPC) remains controversial. This is best exemplified by the original cell posited by Asahara and colleagues to be an EPC in 1997,¹ which has now been clearly phenotyped as a monocyte with dendritic features.² There remains a viable candidate known as the endothelial colony-forming cell (ECFC) or endothelial outgrowth cell (OEC), named because it cannot be seen in ex vivo culture for at least 10 days. These cells proliferate in culture, form a cobblestone monocellular layer, and form networks in ex vivo assays. Given the lack of understanding of previous candidate cells we sought to better characterise the EOC. Here we present data from electron microscopy studies, immunohistochemistry, ligand stimulation studies, and mRNA microarrays

that demonstrate the EOC is a true endothelial cell. Furthermore we demonstrate that these cells can potentially be used as endothelial surrogates in patients with pulmonary hypertension due to a mutation in the bone morphogenetic protein type II receptor (BMPRII). Cells taken from the peripheral blood of patients have a deficiency in intracellular signalling in the BMPRII pathway on stimulation with BMP9. This can be demonstrated by reduced phosphoSmad 1/5 protein on western blotting, and downstream with reduced Id1 gene induction by qPCR. Therefore regardless of its origin and biologically intended function, the EOC is an endothelial cell, and has the capacity to act as an easily derivable endothelial surrogate from patients in whom vascular tissue is not normally obtainable.

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S68 INHIBITION OF P38 MITOGEN ACTIVATED PROTEIN KINASE (MAPK) PREVENTS THE DEVELOPMENT OF EXPERIMENTAL PULMONARY HYPERTENSION

doi:10.1136/thoraxjnl-2011-201054b.68

¹A C Church, ¹R Wadsworth, ²G Bryson, ¹D J Welsh, ¹A J Peacock. ¹Scottish Pulmonary Vascular Unit, Glasgow, UK; ²Department of Pathology, Southern General Hospital, Glasgow, UK

Introduction p38 MAPK has been linked to the pathobiology of pulmonary hypertension (PH) but its role has not been fully investigated. We have previously highlighted the importance of the p38 MAPK pathway in the proliferative response of pulmonary artery fibroblasts to hypoxia. In addition, the BMPR2 mutations seen in PH can lead to increased signalling through the p38 MAPK pathway. These findings suggest p38 MAPK may be an appropriate target for the treatment of PH.

Methods We undertook an in vivo prevention study on male Sprague-Dawley rats that were exposed to hypobaric hypoxia (at 550 mm Hg=10% FiO₂) for a period of 2 weeks. Five animals were dosed daily via an intraperitoneal route, with SB-203580, a p38 MAPK specific inhibitor, and a further five animals acted as controls. After 2 weeks the animals had right ventricular systolic pressure (RVSP) measured,

Abstract S68 Figure 1 RV/LV+septum ratio.

degree of right ventricular hypertrophy (RVH) assessed and lung histology analysed for evidence of vascular remodelling. The lungs were stained with α -smooth muscle actin and the degree of distal muscularisation in vessels <80 mm in diameter assessed. Results were analysed with appropriate statistical tests.

Results There was a significant difference in the RVSP between groups (control 37.09 mm Hg $\pm$ 5.09 vs drug 20.59 mm Hg $\pm$ 3.19; $p=0.025$). There was less RVH (control 0.38 vs drug 0.25; $p=0.0032$) in the drug treated group (see Abstract S68 figure 1) and the total RV weights were also less (control 147 mg vs drug 109 mg; $p=0.018$). There was no difference in haematocrit between groups. There was less pulmonary vascular remodelling as indicated by a reduction of fully muscularised and an increase in non-muscularised vessels observed in the drug treated group ($p<0.001$).

Conclusion We have shown in a chronic hypoxic model of PH that by inhibiting the p38 MAPK pathway in vivo the development of pulmonary hypertension can be prevented. This suggests that the p38 MAPK pathway could be a potential therapeutic target for PH. Further studies are warranted, in particular to see if inhibition can reverse established disease.

S69 SERUM OSTEOPROTEGERIN PREDICTS MORTALITY IN A PROSPECTIVE STUDY ON INCIDENT CASES OF PULMONARY ARTERIAL HYPERTENSION

doi:10.1136/thoraxjnl-2011-201054b.69

¹R Condliffe, ²J Pickworth, ²K Hopkinson, ²A Hameed, ³S Walker, ¹C Elliot, ²S Francis, ²C Newman, ³D Crossman, ³A Morton, ¹D Kiely, ²A Lawrie. ¹Royal Hallamshire Hospital, Sheffield, UK; ²University of Sheffield, Sheffield, UK; ³NIHR Sheffield Cardiovascular Biomedical Research Unit, Sheffield, UK

Background and Objectives Despite improvements in the overall management of Pulmonary Arterial Hypertension (PAH) the disorder still causes significant morbidity and mortality. Current treatments fail to reverse the disease, and clinical assessment does not always differentiate between, or reflect, the local pathogenesis within the heart or pulmonary circulation. Current proposed biomarkers, for example, brain natriuretic peptide (BNP and NT-proBNP), largely reflects myocardial rather than pulmonary vascular remodelling. Subsequently, there has been increasing interest in identifying a biomarker for PAH that can track with lung pathology, and treatment. Through our desire to understand disease pathogenesis, our studies in vitro and in animal models have identified osteoprotegerin (OPG) as a candidate biomarker. We have previously reported that OPG was elevated in a prevalent cohort of patients with IPAH. The aim of this study was to verify the utility of OPG as a biomarker for PAH in a second cohort of incident cases and assess the effect of treatment at follow-up visits.

Methods Serum samples were obtained from 35 patients with IPAH, 26 patients with CTD-PAH and 65 age-matched controls. Serum OPG concentrations were measured by ELISA, correlations with pulmonary haemodynamics, routine clinical biochemistry and prognostic significance were then assessed.

Results OPG concentrations were significantly elevated in IPAH (mean 4485 pg/ml) and CTD-PAH (3824 pg/ml) compared to controls (1749 pg/ml). Concentrations of OPG correlated positively with pulmonary vascular resistance (PVR) and WHO functional class and negatively with the incremental shuttle walk test (ISWT). An OPG concentration above 4744 pg/ml predicted poorer survival. OPG was significantly lower in patients at follow-up after the commencement of targeted PAH therapies.

Conclusion PAH is characterised by elevated serum OPG and this correlates with functional class and PVR. Perhaps most importantly high serum levels of OPG predict a poor outcome. Further longitudinal work is required, and is currently underway to further validate these findings.

S70 DIAGNOSTIC UTILITY AND PROGNOSTIC VALUE OF QUANTITATIVE CARDIAC MR INDICES IN PATIENTS WITH SUSPECTED PULMONARY HYPERTENSION

doi:10.1136/thoraxjnl-2011-201054b.70

¹A J Swift, ¹S Rajaram, ²R Condliffe, ¹D Capener, ³C Hill, ³C Davies, ²J Hurdman, ²C Elliot, ¹J M Wild, ²D G Kiely. ¹University of Sheffield, Sheffield, UK; ²Sheffield Pulmonary Vascular Disease Unit, Sheffield, UK; ³Radiology Department, Hull and East Yorkshire Hospitals NHS Trust, Sheffield, UK

Introduction and Objectives The aim of this study was to assess the clinical utility of quantitative MR indices of cardiac morphology and function in a large cohort of patients with pulmonary hypertension (PH).

Methods We retrospectively studied 233 consecutive patients with suspected PH who underwent cardiac MRI and right heart catheterisation (RHC) within 48 h. Four chamber and short axis (SA) CINE images were acquired using cardiac gated multi-slice imaging with a steady state free precession sequence at 1.5T. The diagnostic and prognostic significance of quantitative measurements of right ventricular morphology and function were assessed.

Results Right ventricular end-diastolic mass index was the measurement with the strongest correlation with mPAP ($r=0.74$) and the highest diagnostic accuracy for the detection of PH (area under the receiver operator curve of 0.91). During the mean follow-up of 18 months (0–36 months), 36 patients with PH died. Right ventricular ejection fraction ($p=0.003$), right ventricular stroke volume index ($p=0.03$) and IVC size ($p=0.01$) were the MR predictors of mortality across the subgroups of PH. MR measurements of right ventricular ejection fraction ($p=0.004$), right ventricular stroke volume index ($p=0.02$), and left ventricular diastolic eccentricity index ($p=0.005$), all predicted mortality in patients with pulmonary arterial hypertension, Abstract S70 figure 1 below shows the Kaplan–Meier plots the MR predictors of mortality in PAH. IVC size ($p=0.018$) was an independent predictor of mortality in the full cohort of patients with PH, and diastolic eccentricity index ($p=0.037$) was an independent predictor of adverse outcome in patients with PAH.

Abstract S70 Figure 1 Kaplan–Meier plots showing the survival curves for patients with PAH above and below the median value of MR derived right ventricular stroke volume index (RVSVI), right ventricular ejection fraction (RVEF) and diastolic eccentricity index (dEI).

Conclusion Cardiac MRI provides a comprehensive assessment of right ventricular morphology and function in patients with PH. This study confirms the diagnostic and prognostic applicability of MRI in unselected patients with PH of varied aetiologies in a practical clinical setting.

S71 INFLUENCE OF AGE ON CLINICAL PHENOTYPES OF INCIDENT IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION. RESULTS FROM THE PULMONARY HYPERTENSION REGISTRY OF THE UK AND IRELAND

doi:10.1136/thoraxjnl-2011-201054b.71

¹Y Ling, ¹M K Johnson, ²D Kiely, ²R Condliffe, ²C Elliot, ³S Gibbs, ³L Howard, ⁴J Pepke-Zaba, ⁴K Sheares, ⁵P Corris, ⁵A Fisher, ⁵J Lordan, ⁶S Gaine, ⁷G Coghlan, ⁸J Wort,