63. Mechanism and monitoring of airway diseases

353
Longitudinal analysis of lung function decline with eosinophilic clustering in severe asthma
Chris Newby, Josh Agbeleti, Beth Hargaudon, Peter Bradding, Andrew Wardlaw, Ian Pavord, Ruth Green, Chris Brightling, Sarah Siddiqui. Department of Infection, Immunology and Inflammation, Institute for Lung Health, University of Leicester, Leicester, United Kingdom

Background: Lung function decline over time is an important variable for patients with severe difficult asthma and it is unclear how granulocytic cell counts in sputum are associated with this variable as few longitudinal studies include both biomarkers.

Aims and objectives: To analyse lung decline, post bronchodilator FEV1 was recorded over time in order to determine the best fitting mixed effect model to determine the role of granulocytes.

Methods: Data was collected from the Glenfield Hospital Severe asthma clinic, the mean duration of follow up and number of visits was 6 years and 2.7 years. A mixed effect model was applied to the data. Using individual patient mean and standard deviation over time, a statistical mixture/cluster analysis was implemented.

Results: For the best fitting mixed effects model FEV1 decline was -25.7 ml/year, p<0.0001. The significant independent fixed effects included exacerbations, age of onset, log eosinophils (p<0.001). Three clusters were found in the log eosinophil cluster analysis. Cluster 1 described a low grade eosinophilic group. Cluster 2, a hyper eosinophilic group and cluster 3, a neutrophilic/non eosinophilic group. The clusters differed in their frequency of exacerbation/decline.

Conclusions: Eosinophils were found to be a significant predictor for FEV1 decline. Clustering eosinophilic variables found that patients are either consistently eosinophilic over time or have a large amount of eosinophilic variation.

354
Sputum eosinophilia identifies systemic corticosteroid responsiveness in acute exacerbations of COPD
Monika Bafadhel1, Susan McCenna1, Sarah Terry1, Vijay Mistry1, Mitesh Pancholi1, David Lomas1, Per Venge2, Mike Barer1, Seh Johnston3, Ian Pavord2, Chris Brightling1. 1Institute for Lung Health, University of Leicester, Leicester, United Kingdom; 2Department of Medical Sciences, Clinical Chemistry, University of Uppsala, Uppsala, Sweden; 3Department of Respiratory Medicine, Centre for Respiratory Infections, Imperial College, London, United Kingdom; 4Cambridge Institute for Medical Research, University of Cambridge, Cambridge, United Kingdom

Introduction: Eosinophilic airway inflammation (EA, >3% sputum eosinophils) during stable chronic obstructive pulmonary disease is associated with corticosteroid responsiveness. Whether this is true during exacerbations remains unknown.

Methods: COPD patients were included in a double blind prednisolone placebo controlled trial. Measurements of airway inflammation, lung function and health status using the chronic respiratory questionnaire (CRQ) and visual analogue scale (VAS) were assessed at baseline, exacerbation and 2 weeks after treatment.

Results: 166 exacerbations were captured from 109 patients (69 men, 40 women). All eosinophilic exacerbations (n=31) were treated with prednisolone. Non eosinophilic airway inflammation (NEA) occurred in 135 exacerbations, of which 70% (n=94) were treated with prednisolone and 30% (n=41) with placebo. Two weeks after prednisolone treated exacerbations, quality of life and lung function improved significantly in those with EA compared to NEA (mean change, 95%CI) in CRQ and FEV1, was 1.3 units (1.1 to 1.5) vs. 0.8 units (0.5 to 1.0) (p<0.001) and 335mL (219 to 451) vs. 102mL (52 to 152) (p<0.001) respectively. VAS returned to baseline earlier in EA exacerbations treated with prednisolone (p=0.016, see figure)

Conclusion: Corticosteroid responsiveness during exacerbations of COPD can be identified by a sputum eosinophilia.

355
Tapering oral corticosteroids in severe asthma is associated with a decrease in fractional exhaled nitric oxide
Simone Hashimoto1, Anneke Ten Brinke1, Jacob K. Sont1, Arleko H. Zwinderman2, Peter J. Sterk2, Elisabeth H. Bel1. 1Respiratory Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands; 2Pulmonology, Medical Center Leeuwarden, Leeuwarden, Netherlands; 3Medical Decision Making, Leiden University Medical Center, Leiden, Netherlands; 4Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands

Rationale: In a recent oral corticosteroid tapering study in patients with severe asthma (Hashimoto ATS 2010), we observed high levels of exhaled nitric oxide (FENO) despite high doses of oral corticosteroids, and, unexpectedly (Smith NEJM 2005), only a minor role of FENO in adjusting the dose.

Hypothesis: Changes in FENO values in patients with severe prednisone-dependent asthma are not associated with changes in corticosteroid dose or clinical parameters.

Methods: 48 adult patients with severe prednisone dependent asthma (mean (SD) age 49.4 (12.2) y; 18 male) were included in this 6 months follow-up study. Relationships between changes in daily FENO or oral corticosteroid dose, asthma control (ACQ), and FEV1 were assessed. Pearson correlation and regression analyses were used.

Results: Baseline median (range) FENO was 38 (5-300) ppb and 0.60 mg/day. Daily changes in FENO from baseline were positively associated with daily changes in prednisone dose (r=0.22, p=0.003) but not with FEV1 (r=0.02, p=0.77) or ACQ (r=0.03, p=0.65).

Conclusion: In contrast to patients with mild-moderate asthma, patients with severe, prednisone dependent asthma show a decrease in FENO levels when prednisone is tapered.

Implication: This suggests that oral corticosteroids may contribute to persistently high levels of FENO in severe asthma.

356
Sputum eosinophil levels in corticosteroid-treated asthmatic patients
Elena Bacci, Manuela Latorre, Silvana Chianchetti, Federico Dente, Antonella Di Franco, Lorenza Melosini, Federica Novelli, Erika Camici, Pierluigi Paggiaro. CardioThoracic and Vascular Department, University of Pisa, Pisa, Italy

We have shown that asthmatic patients, despite being asymptomatic after 1 month treatment with inhaled corticosteroids (ICS), may have persistent sputum eosinophilia associated with higher degrees of bronchial hypersensitivity (Bacci et al., ATS meeting 2010). In order to test the effects of longer treatment periods, we treated 116 symptomatic, steroid-naïve, mild-to-moderate asthmatic patients with different doses of ICS (50 to 500 mg bid) for three to six months. Before and after treatment, all patients underwent spirometry, methacholine test, sputum analysis, and recorded symptom score (SS) and Peak Expiratory Flow (PEF) throughout the study period. Regardless of treatment dose and duration, some patients (n=56) still had high (≥2%) sputum eosinophils after ICS treatment; they were no different from patients with low sputum eosinophils as regards clinical and functional data after treatment, but had higher baseline SS (1.5 [0.1-3.6] vs 1.0 [0.1-3.1], p=0.04). After treatment, some patients still had high sputum eosinophils despite being totally controlled (SS<0), they were no different from totally controlled patients with low sputum eosinophils.

We conclude that, in patients with greater symptom levels before treatment, sputum eosinophilia may persist despite ICS treatment. Also, sputum eosinophilia may persist even in patients with totally controlled asthma, but after 6 months the...
Aims: To compare biomarker-directed prednisolone therapy to current standard treatment during COPD exacerbations

Methods: Patients with COPD exacerbations were randomised to receive standard therapy (ST) or a biomarker directed therapy (BT). BT patients were given prednisolone when the blood eosinophil count was ≥2% (biomarker positive) and placebo when ≤ 2% (biomarker negative) (see figure).

Results: From 109 patients; 86 exacerbations were treated in the BT group and 80 in the ST group. Prednisolone prescription was reduced by 49% (95% CI 38 to 56%). From 109 patients; 86 exacerbations were treated in the BT group and 80 in the ST group. Placebo administration < 8 mg/day was increased by 20% (24% vs. 36%) (p=0.001) in the BT compared to ST group. There was no difference between groups in health status or FEV1 after 14 days treatment. Placebo administration < 80 in the ST group. Prednisolone prescription was reduced by 49% (95% CI 38 to 56%).

Conclusions: A phenotype-specific biomarker approach can safely and effectively be applied to prednisolone therapy during exacerbations.

358 Relationship between exhaled nitric oxide and exacerbation frequency in COPD patients: A longitudinal study

Balazs Antus1,2, Szabolcs Soter1,2, Imre Barta1,2

Department of Pathophysiology, National Korányi Institute of TB and Pulmonology, Budapest, Hungary; 2Department of Pathophysiology, National Korányi Institute of TB and Pulmonology, Budapest, Hungary

We previously demonstrated that fractional exhaled nitric oxide (FENO) level determined at hospital admission predicts response to treatment in COPD patients hospitalized with acute exacerbations. The optimum cut point for FENO was 27 ppb. In this longitudinal study we assessed the relationship between FENO and frequency of hospitalization-associated exacerbations in patients with COPD.

66 COPD patients (mean age: 65.6 ± 1.4 years; 31 males, 35 females) with FENO level lower (n=29; group 1) or higher (n=27; group 2) than 27 ppb were followed over a 33.9 ± 0.9 months period of time. In patients in group 2 the exacerbation frequency (1.0 ± 0.19 vs. 0.37 ± 0.09 exacerbations/patient-year; p<0.05) and the number of hospitalization days due to exacerbations (18.5 ± 3.9 vs. 6.9 ± 1.0 hospitalization days/patient-year; p<0.05) were reduced compared to group 1.

Moreover, there was a trend towards increased time-to-first exacerbation (6.9 ± 1.5 vs. 8.2 ± 2.3 months; p<0.05) in these patients. In patients in group 1 positive sputum culture results were more often obtained (group 1: 24 pos. and 15 neg. vs. group 2: 9 pos. and 18 neg.; p<0.05) and the need for intensive care was more frequently indicated. Severity of COPD as assessed by GOLD stages was not significantly different between the two subgroups of patients (p<0.05).

Our data suggest that the rate of exacerbations requiring hospitalization is reduced in COPD patients who have higher (≥27 ppb) FENO level during exacerbation. FENO may have a role in detecting different COPD phenotypes.

359 Expression of superoxide dismutases and its association to inflammatory cells in small airways of COPD patients

Beata T. Olejniczak1,2, Stefan Marklund1, Cecilia Andersson2, Michiko Morii3, Andrej Rubuj1, Claus-Goran Löfdahl1, Jonas Erjefält1, 1Department of Medicine, Trelleborg Hospital, Lund, Sweden; 2Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 3Clinical Chemistry Department of Medical Biosciences, University College, Clinical Chemistry, Umeå, Sweden; 4Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 5Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 6Department of Cardiology, Medical University of Lublin, Medicine, Lublin, Poland; 7Department of Respiratory Medicine and Allergology, Lund University Hospital, Medicine, Lund, Sweden; 8Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden

Background and aims: Chronic obstructive pulmonary disease (COPD) is predominantly a result of the cumulative exposure to tobacco smoke and its progression is stimulated by oxygen-derived free radicals from tobacco smoke or activated structural and inflammatory cells. Superoxide dismutases (SODs) are the first line of antioxidants defence system. The present study investigates the expression of SOD and their association to inflammatory cells and local destructive index (DI) in small airways of non-smokers and patients with severe COPD.

Methods: Expression of macrophages, mast cells, neutrophils, and SODs (CuZn-SOD, Mn-SOD, EC-SOD) was evaluated by immunohistochemistry using formalin-fixed, paraffin-embedded sections from non-smoking controls (n=9) and COPD patients (n=10). Histological and immunohistochemical analyses were performed using the same Region-Of-Interest within each small airway.

Results: The mean percentage and intensity of CuZn-SOD-immunoreactive cells were greater in COPD patients (p<0.05) and with a predominant expression in the small airway epithelium whereas epithelial Mn-SOD and EC-SOD expression was not altered. The DI was negatively correlated with SODs immunoreactivity. Macrophages were prominently present in the alveolar region and neutrophils in small bronchioles. Mast cells were prominent in both small airways and alveolar parenchyma, although the total numbers were lower than in COPD patients.

Conclusions: We demonstrate overexpression of CuZn-SOD and the elevated number of inflammatory cells. A correlation has been shown between SODs immunoreactivity and DI.

360 Disease expression in patients with primary ciliary dyskinesia (PCD), CF and pancreatic sufficiency (CF-PS) and insufficiency (CF-PI)

Malena Cohen-Cymborowski1, Natalia Simonovsk1,2, Nathur Hillier1, Alexis Tilles-Hillier1,2, David Shoevers5,6, Eitan Keren1,2,3, 1CF and PCD Center, Hadassah Hebrew University Medical Center, Jerusalem, Israel; 2Pediatrics, Hadassah Hebrew University Medical Center, Jerusalem, Israel; 3Radiology, Hadassah Hebrew University Medical Center, Jerusalem, Israel

In both CF and PCD, lung disease is caused by impaired mucociliary clearance. In CF it is a result of airway surface liquid depletion and in PCD, of ciliary defects in small airways of COPD patients

In both CF and PCD, lung disease is caused by impaired mucociliary clearance. In CF it is a result of airway surface liquid depletion and in PCD, of ciliary defects in small airways of COPD patients

We previously demonstrated that fractional exhaled nitric oxide (FENO) level determined at hospital admission predicts response to treatment in COPD patients hospitalized with acute exacerbations. The optimum cut point for FENO was 27 ppb. In this longitudinal study we assessed the relationship between FENO and frequency of hospitalization-associated exacerbations in patients with COPD.

66 COPD patients (mean age: 65.6 ± 1.4 years; 31 males, 35 females) with FENO level lower (n=29; group 1) or higher (n=27; group 2) than 27 ppb were followed over a 33.9 ± 0.9 months period of time. In patients in group 2 the exacerbation frequency (1.0 ± 0.19 vs. 0.37 ± 0.09 exacerbations/patient-year; p<0.05) and the number of hospitalization days due to exacerbations (18.5 ± 3.9 vs. 6.9 ± 1.0 hospitalization days/patient-year; p<0.05) were reduced compared to group 1.

Moreover, there was a trend towards increased time-to-first exacerbation (6.9 ± 1.5 vs. 8.2 ± 2.3 months; p<0.05) in these patients. In patients in group 1 positive sputum culture results were more often obtained (group 1: 24 pos. and 15 neg. vs. group 2: 9 pos. and 18 neg.; p<0.05) and the need for intensive care was more frequently indicated. Severity of COPD as assessed by GOLD stages was not significantly different between the two subgroups of patients (p<0.05).

Our data suggest that the rate of exacerbations requiring hospitalization is reduced in COPD patients who have higher (≥27 ppb) FENO level during exacerbation. FENO may have a role in detecting different COPD phenotypes.

Conclusions: A phenotype-specific biomarker approach can safely and effectively be applied to prednisolone therapy during exacerbations.

359 Expression of superoxide dismutases and its association to inflammatory cells in small airways of COPD patients

Beata T. Olejniczak1,2, Stefan Marklund1, Cecilia Andersson2, Michiko Morii3, Andrej Rubuj1, Claus-Goran Löfdahl1, Jonas Erjefält1, 1Department of Medicine, Trelleborg Hospital, Lund, Sweden; 2Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 3Clinical Chemistry Department of Medical Biosciences, University College, Clinical Chemistry, Umeå, Sweden; 4Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 5Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden; 6Department of Cardiology, Medical University of Lublin, Medicine, Lublin, Poland; 7Department of Respiratory Medicine and Allergology, Lund University Hospital, Medicine, Lund, Sweden; 8Department of Experimental Medical Science, Lund University, Med Science, Lund, Sweden

Background and aims: Chronic obstructive pulmonary disease (COPD) is predominantly a result of the cumulative exposure to tobacco smoke and its progression is stimulated by oxygen-derived free radicals from tobacco smoke or activated structural and inflammatory cells. Superoxide dismutases (SODs) are the first line of antioxidants defence system. The present study investigates the expression of SOD and their association to inflammatory cells and local destructive index (DI) in small airways of non-smokers and patients with severe COPD.

Methods: Expression of macrophages, mast cells, neutrophils, and SODs (CuZn-SOD, Mn-SOD, EC-SOD) was evaluated by immunohistochemistry using formalin-fixed, paraffin-embedded sections from non-smoking controls (n=9) and COPD patients (n=10). Histological and immunohistochemical analyses were performed using the same Region-Of-Interest within each small airway.

Results: The mean percentage and intensity of CuZn-SOD-immunoreactive cells were greater in COPD patients (p<0.05) and with a predominant expression in the small airway epithelium whereas epithelial Mn-SOD and EC-SOD expression was not altered. The DI was negatively correlated with SODs immunoreactivity. Macrophages were prominently present in the alveolar region and neutrophils in small bronchioles. Mast cells were prominent in both small airways and alveolar parenchyma, although the total numbers were lower than in COPD patients.

Conclusions: We demonstrate overexpression of CuZn-SOD and the elevated number of inflammatory cells. A correlation has been shown between SODs immunoreactivity and DI.