370. Biomarkers and exacerbations of asthma and COPD

P3348
Monitoring PGD2 production in airway disease
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Introduction: Prostaglandin (PG) D2 is a major mast cell mediator implicated in asthma and airway disease. Measurement of the urinary levels of 9α,11β-PGF2α has been established to monitor PGD2 production. Tetranor prostaglandin D (PGDM) is however the major urinary metabolite of PGD2.

Aims and objectives: To evaluate the use of urinary levels of 9α,11β-PGF2α vs. PGDM. In addition, the use of enzyme immune assay (EIA) was compared with LC-MS/MS.

Methods: Urinary samples from four studies were used; bronchoprovocation using allergen (n=8) and aspirin in aspirin-intolerant asthma (n=11), effect of celecoxib on baseline excretion (n=19), and excretion in patients with mastocytosis or anaphylaxis (MA) during exacerbation (n=15). Urinary excretion of 9α,11β-PGF2α and PGDM were measured by specific ELISAs (Cayan Chemical) and LC-MS/MS, and data expressed as ng/mmol creatinine.

Results: The levels of PGDM (mean±SEM) before allergen challenge were 1330±348 and 1236±192 after (p<0.05), the corresponding values of 9α,11β-PGF2α were 40±4 and 77±10 (p=0.002), respectively.

With aspirin challenge levels of PGDM were 516±82 before and 609±95 after (p<0.05), whereas the levels of 9α,11β-PGF2α were 56±16 and 75±24 (p=0.002), respectively.

In MA the levels of PGDM and 9α,11β-PGF2α were 1977±886 (p<0.005 for PGDM vs baseline in healthy subjects) and 251±66 respectively, with values mildly correlated (r=0.698, p=0.00382).

Bland-Altman analysis showed good agreement between PGDM measurements with MS and ELA.

Conclusion: The earlier metabolite 9α,11β-PGF2α may be more suitable to follow the dynamics of release during challenges whereas the higher levels of PGDM may be more appropriate for monitoring global differences in baseline production of PGD2.

P3349
Antibiotics in exacerbations of asthma
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Introduction: Current guidelines explicitly do not recommend prescribing antibiotics as asthma exacerbations. We aimed to assess the prescription rate of antibiotics related to asthma exacerbations in primary care and to provide patient characteristics associated with antibiotic treatment.

Methods: We retrieved all electronic patient records concerning acute asthma in adults during 2008 recorded amongst 149,279 patient contacts by the general practitioners and patient characteristics were analyzed using the clinical parameters documented by GPs of patients who received antibiotics.

Results: Of 540 identified exacerbations, 108 (20%) were treated with antibiotics, of which in 16 cases (15%) a suspicion of pneumonia was documented. Univariate and multivariate analyses we analyzed the clinical parameters documented by GP’s of patients who received antibiotics.

Conclusion: The antibiotic prescription rate for asthma exacerbations was low. However, certain patient characteristics were associated with antibiotic treatment.

Table 1. Clinical associates of antibiotic treatment

<table>
<thead>
<tr>
<th>History</th>
<th>p-value</th>
<th>Examination</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>&lt;0.002</td>
<td>Ill appearance</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sputum</td>
<td>&lt;0.001</td>
<td>Fever</td>
<td>0.023</td>
</tr>
<tr>
<td>Common cold</td>
<td>0.178</td>
<td>Rhinitis</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptoms of the ear</td>
<td>0.019</td>
<td>ENT problems</td>
<td>0.050</td>
</tr>
<tr>
<td>Symptoms &gt; 3 days</td>
<td>0.261</td>
<td>Focal abnormalities on auscultation</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;0.001</td>
<td>Wheezing</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Conclusion: Antibiotics are prescribed more often for asthma exacerbations by GPs than proposed by international guidelines. Fever appears to be a major trigger for antibiotic therapy, in contrast to recommended care. This suggests that overprescription of antibiotics for asthma exacerbations is prevalent.

P3350
Monitoring free serum IgE in severe asthma patients treated with omalizumab
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It is stated that benefit of omalizumab treatment in severe IgE-dependent asthma requires serum free IgE concentrations below 50 ng/ml. It is unclear if monitoring free serum IgE is clinically meaningful once omalizumab treatment is initiated.

Free IgE and omalizumab serum concentrations were quantified in 22 patients with severe asthma (68% female, 47±11 yrs, mean (±SD) pre-bronchodilator FEV1 62±13%, baseline mean (±SEM) free serum IgE 652±136 ng/ml) treated with omalizumab for 4 months using a Recovery-ELISA. Bland-Altman analysis showed good agreement between PGDM measurements with MS and ELA.

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stop treatment. The relevance of free IgE measurements is limited to demonstrating an adequate reduction in those responders. These results question the free IgE target range postulated to be necessary for a treatment response.

P3351
Serum immunoglobulin E level is a useful marker for the risk of opportunistic infection in steroid dependent patients with chronic inflammatory airway diseases

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Aim: Patients with chronic inflammatory airway diseases such as severe asthma, pulmonary fibrosis often need to have long-term oral corticosteroids (O-CS). Patients who are administered O-CS, even a small amount, are susceptible for opportunistic pneumocystis pneumonia, fungal infection, herpes-zoster infection. The aim of this study is to clarify the usefulness of serum IgE as a marker for risk of OI in patients with long-term O-CS therapy.

Methods: Seventeen patients with respiratory diseases (severe asthma 11, pulmonary fibrosis 5, Chung-Stauss syndrome 1) taking regular-use of O-CS were enrolled to this study. We retrospectively reviewed the medical records and collected the data about incidence of OI and serum IgE levels of the patients.

Results: Seven out of 17 patients suffered from OI. The average IgE level in patients with OI (623±154 mg/dl, n=7) was significantly lower than patients without OI (879±188 mg/dl, p-value<0.01). The area under the ROC curves was 0.87. The most reliable cut-off level was 725 mg/dl with specificity 75%, sensitivity 75%, positive predictive value 86% and negative predictive value 80%.

Conclusion: Serum IgE need to be monitored when patients were given O-CS. It is crucial to keep serum IgE levels more than 725 mg/dl to prevent OI.

P3352
Effects of omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma

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Allergic asthma is a chronic inflammatory airway disease in which immunoglobulin E (IgE) and eosinophils play important pathogenetic roles. We investigated the effect of the anti-IgE antibody omalizumab on markers of eosinophilic inflammation in patients with severe allergic asthma eligible for omalizumab treatment according to current guidelines. In a multi-centre, prospective, open-label, parallel-group trial, 45 patients (19 female, 48±11 yrs, 78±12 kg, 274±228 IU/ml total IgE, FEV1 at baseline 1.8±0.6 L, 61.8±19.5% pred.) received omalizumab (median 450 mg/month) and were administered ICS as add-on therapy. Exhaled nitric oxide (NO), peripheral blood eosinophils and serum interleukin-5 were measured before and after 16 weeks of treatment. In all patients total daily doses of inhaled and oral corticosteroids remained stable during treatment.

23 (74%) patients responded to therapy (GETTE). Baseline NO was 43±8 ppb (mean±SEM) for responders (R) and 23±6 ppb for non-responders (NR), blood eosinophils were 0.39±0.07µl (R) and 0.25±0.06µl (NR), and IL-5 was 7.5±1.1 3 and 1.9±1.5 pg/ml (NR). R vs. NR p=0.030. After 16 weeks NO decreased by 3±6 ppb (R, p=0.804) and 12±18 ppb (NR, p=0.375), blood eosinophils were unchanged (Rweek=week16: -0.14±0.6µl, p=0.687; NR: 0.01±0.04µl, p=0.001), and IL-5 decreased by 3.7±1.0 pg/ml (R, p=0.012) and 0.3±1.4 pg/ml (NR, p=0.625).

In conclusion, patients with a clinical response to omalizumab had higher pre-treatment serum IL-5 levels and a pronounced decrease in serum IL-5 following omalizumab. Blood eosinophils were unchanged, and exhaled NO was low prior and on treatment with omalizumab, consequent to high-dose ICS treatment.

P3354
Reduction in incidence of exacerbations in patients with Alpha 1 antitrypsin deficiency (A1ATD) treated with concentrations of Alpha 1 antitrypsin (A1AT): RXA study

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Introduction: Augmentation therapy with plasma derived Alpha 1 Antitrypsin represents the only specific treatment for patients with Alpha 1 Antitrypsin Deficiency. The aim of this study was to demonstrate that augmentation therapy can reduce the number of exacerbations in patients with A1ATD.

Material and methods: Retrospective multicenter study. We included 127 patients who received augmentation therapy for 18 months and with clinical follow-up for 18 months before treatment. We compared the incidence of exacerbations into the two periods.

Results: 127 patients, 63% male, age:52y, former smokers:79.4%, never smokers:17.4%, PIZZ:93.6%. Basal FEV1:1.24L (±0.5). Patients were treated with Prolastin® (53.5%) or Trypsin® (46.5%), 78% every 21 days. 52 days patients did not present exacerbations in pretreatment period. Augmentation therapy was associated with reduction of 2.4 exacerbations for every ten treated patients in total population and 6 exacerbations for every 10 treated patients in those with previous exacerbations. (Figure 1) Untreated patients have between 1.4 and 4 times more risk of exacerbation than treated patients. We didn't observe differences between both available A1AT products.

Conclusions: Augmentation therapy in the A1ATD reduces the total number of exacerbations with low frequency of adverse events. Study realized with Grifols support.

P3355
Efficacy of roluflamist in the frequent exacerbation COPD phenotype

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Background: COPD exacerbations (EXs) are associated with increased morbidity, mortality and disease progression. The ECLIPSE study showed the best predictor of future EXs is a history of EXs, identifying a frequent exacerbator phenotype maintained over time. Roluflamist (ROF) reduces EX rate in frequent exacerbators, but its relative effect in this phenotype is not known.

Methods: In a post-hoc pooled analysis of 2 of 1 yr studies of ROF 500g in pts with severe COPD, chronic bronchitis and a history of EXs, pts were classified as frequent (≥2 events) or infrequent (1 event) exacerbators based on moderate/severe EX history in the previous yr. EX frequency status was analysed in ROF- and placebo (PBO)-treated pts at baseline and at yr 1.

Results: Among ROF-treated frequent exacerbators (n=413), 32.0% still had frequent EXs at yr 1 vs 40.8% of PBO-treated pts (n=417; RR=0.799, p=0.0148). Among infrequent exacerbators, 17.5% of ROF-treated pts (n=1124) had ≥2 EXs at yr 1 vs 22.9% of PBO-treated pts (n=1137; RR=0.768, p=0.0018). This reduction was similar when considering concomitant LABA, previous ISC treatment or severe EXs leading to hospitalisation/death. When analysed by COPD severity, 26.4% of ROF-treated frequent exacerbators with severe COPD (FEV1 30–50% predicted, n=246) still had frequent EXs at yr 1 vs 38.9% of PBO-treated pts (n=239; RR=0.683, p=0.0042); the percentage of frequent exacerbators was reduced by ≥2 EXs at yr 1 vs baseline, regardless of treatment condition.

Conclusions: This analysis shows that ROF shifts pts from the frequent to the more stable infrequent exacerbator state. This effect was not seen in frequent exacerbators with very severe COPD, highlighting the need for early treatment initiation.

P3356
Modelling and simulation in successful drug development programmes: Characterisation of exacerbation reduction with roluflamist to corroborate the importance of defining patient subtypes in COPD

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Background/Rationale: Roluflamist (ROF), an oral, selective PDE4 inhibitor, reduces the rate of exacerbations and improves lung function in severe COPD. During clinical development, modelling and simulation techniques were used to identify and confirm a paradigm to explore patient, disease and treatment covariates. This approach identified patient populations that will benefit most from ROF, and was used to help design confirmatory clinical trials.

Methods: Data from two 1-year, randomised, double-blind, placebo-controlled, parallel-group trials [Rennard S, et al. Respir Exp 2011;12(1):18] in 2686 patients were used to build exacerbation and lung function models to identify patient characteristics that significantly impacted the clinical endpoints.

Results: Patients with chronic bronchitis, higher cough/sputum scores, concomitant ICS use and low predicted FEV1 at baseline were identified as having a higher rate of exacerbations and treatment effect. Patient characteristics as defined by the models were used, in addition to a history of exacerbations, to simulate the design of two other 1-year clinical trials [Calverley PMA, et al. Lancet 2009;374:685-94].

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Clonal implications of serum procalcitonin in acute exacerbations of chronic obstructive pulmonary disease

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Background: A reliable test for differentiation between bacterial and nonbacterial AECOPD would be extremely helpful in management of AECOPD.

Objective: To explore the diagnostic and prognostic role of serum procalcitonin (PCT) in AECOPD

Methods: A total of 100 patients with AECOPD and 20 of healthy individuals were studied. On presentation, serum PCT concentration was measured, and quantitative sputum culture was performed for AECOPD. The patients were reevaluated when they had reached their stable clinical state. Pathogenic bacterial microorganism (PEM) was regarded as significant if they were ≥10^5 CFU/mL. The patients were classified into two subgroups: group A, patients with bacterial AECOPD (n=40), and group B, patients with nonbacterial AECOPD (n=60).

Results: On presentation, the levels of PCT for patients of group A (1.59±0.52 μg/L) were significantly greater than patients of group B [0.11±0.02 μg/L] and control group [0.75±0.03 μg/L]. When they had reached their stable state, the levels of PCT for patients of group A [0.12±0.4 μg/L], which was significantly lower than in exacerbation [11.59±0.52 μg/L], but in patients of group B the levels of PCT did not change [0.1±0.01 μg/L]. In the stable state, there were no differences in the levels of PCT between the two subgroups as well as between patients and control. Furthermore, a significant correlation was recorded between PCT levels in group A at time of presentation and temperature (r=0.988, p<0.05), leucocytic count (r=0.897, p<0.05), and FEV1% of predicted (r=0.889, p<0.05).

Conclusion: In patients presented with AECOPD, PCT is an excellent diagnostic and prognostic marker of bacterial infection.

Efficacy and safety of bacterial lysates in patients with chronic obstructive pulmonary disease and exacerbations

Hao Tang, Zheng Fang, Qingyu Xiu, on behalf of the Broncho-Vaxom Study Group.

Objective: This study was a double-blind, placebo-controlled, randomized clinical trial to evaluate the preventive effect of bacterial lysates (Broncho-Vaxom, OM-85 BV) on acute exacerbations in patients with COPD or chronic bronchitis in China.

Methods: 428 patients recruited from 13 centers were randomly allocated into BV or placebo. 384 patients completed the study (192 OM-85 BV group and 192 in the placebo group). Patients received medications for 10 days per month during 3 months with a 10-week follow-up.

Results: This study revealed that the proportion of patients with recurrent exacerbation in OM-85 BV group was significantly lower than that in placebo group within 12-week treatment period (24.4% vs. 33.3%, p<0.05). Among all subjects having exacerbation (≥1 time), the percentage of patients with recurrent exacerbation (≥2 times) was significantly lower in OM-85 BV group than that in placebo group during the 12-week treatment period (38.7% vs. 73.1%, p<0.01). The percentage of concomitant antibiotics was significantly lower in OM-85 BV group than that in placebo group (37.0% vs. 63.0%, p<0.05). In terms of safety, there was no significant difference between the two groups in the incidence of adverse events (27.9% in BV group vs. 27.7% in placebo group, p<0.05).

Conclusions: OM-85 BV significantly reduced the rate of recurrent exacerbations in patients with chronic bronchitis or COPD in therapy period. It also significantly reduced the frequency of exacerbations in individual patients in active therapy period and decreased the usage of antibiotics, with a good safety profile.

p-blockers and risk of COPD exacerbation requiring hospitalisation in patients with COPD

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Background: In the past, p-blockers were contra-indicated in COPD. Recent evidence, including a cohort study by Rutten et al. (Arch Intern Med 2010), suggests that p-blockers produce good outcomes in COPD. This degree of protection might be biased.

Objectives: To study the effect of p-blockers on the risk of severe COPD exacerbations.

Methods: We conducted several analyses to study the effect of p-blockers on COPD exacerbations by: 1) mimicking the cohort design of Rutter et al. 2) avoiding

immortal time and exposure bias through a nested case-control study in a COPD cohort and 3) reducing confounding by indication by restricting the case-control analyses to users of p-blockers during follow-up. Data from the Dutch IPCI GP database (2000 to 2007) were used. Cases were all COPD patients with a first COPD exacerbation requiring hospitalization. To each case, controls were matched on age, sex, and indexdate. Cox proportional hazard and conditional logistic regression analyses were used.

Results: Within the cohort of 6788 COPD patients, 619 patients had a COPD exacerbation requiring hospitalization. Current use of p-blockers significantly reduced the risk of severe COPD exacerbation in the cohort analysis (HRadj=0.73, 95%CI 0.60-0.90). We also conducted a case-control analysis of COPD exacerbation requiring hospitalization. The risk was 40% (ORadj 0.60, 95% CI 0.44-0.82). When controlling for confounding by indication, the protective effect remained statistically significant (ORadj 0.87, 95% CI 0.52-1.45). In patients with co-existing heart failure, a significant protective effect was observed (ORadj 0.15, 95% CI 0.03-0.80).

Conclusions: The choice of study design is crucial when assessing the effect of p-blockers on COPD outcomes.

Skin sensitivity to corticosteroids is associated with COPD susceptibility


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Introduction: Inhaled corticosteroids (ICS) improve symptoms, exacerbation rates and quality of life in COPD. However, not all COPD patients benefit from ICS treatment. Corticosteroid sensitivity can be studied with the skin blanching test, where topical corticosteroids cause local vasoconstriction. We investigated in young and old individuals if skin response to corticosteroids is associated with susceptibility to develop COPD.

Methods: Young (18 - 40 years) healthy subjects who were non-susceptible or susceptible to develop COPD (n=19 and 14 resp.), and older (40-75 years) subjects without and with COPD (n=15 and 47 resp.) were included. Susceptibility in young subjects was based on a high prevalence of COPD in smoking family members of these subjects. Budesonide dissolved in 95% ethanol was applied to the skin in eight concentrations (0-1000 μg/ml). Blanching was scored with a 7-point scale: 0 (no blanching) and 3 (intense blanching).

Results: Young non-susceptible subjects showed higher blanching scores compared to all groups (figure 1). In COPD patients, a lower blanching score correlated with lower FEV1/FVC ratio (B=-0.017, p<0.01) and higher GOLD stage (figure 2).

Conclusions: These preliminary data suggest that relative corticosteroid insensitiv- ity contributes to COPD development and progression.

Inhaled corticosteroids in patients with mild to moderate COPD with and without airway hyperresponsiveness to mannitol: A randomized placebo controlled trial

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Background: Based on former data airway hyperresponsiveness (AHR) to manni tol challenge could allow to identify a subgroup of subjects who will respond to treatment with ICS.

Methods: We investigated 68 subjects with mild to moderately severe COPD. All subjects were treated with tiotropium initiated 4 weeks prior to randomisation. Subjects were randomized to either budesonide (daily dose of 1600 mcg) or placebo for 3 months. At all visits lung function, quality of life (SGRO), AHR to mani tol, exhaled nitric oxide (NO) and MRC were assessed. AHR was defined as a 15% fall in FEVI at < or = 635 mg (PD15). RDR was calculated as the percent fall in FEVI at the last dose divided by totally dose of mannitol administered.

Results: There was no significant change from baseline of FEVI1 pred. (2.46 ± 0.5% CI [-1; 5.9] p= 0.162), quality of life (SGRO) (-3.21 ± 95% CI [-8.5; 2.1] p= 0.04), and FEV1% of predicted (r=0.889, p<0.05). There was no significant change from baseline of FEV1% pred. (2.46 ± 0.5% CI [-1; 5.9] p= 0.162), quality of life (SGRO) (-3.21 ± 95% CI [-8.5; 2.1] p= 0.04), and FEV1% of predicted (r=0.889, p<0.05). There was no significant change from baseline of FEV1% pred. (2.46 ± 0.5% CI [-1; 5.9] p= 0.162), quality of life (SGRO) (-3.21 ± 95% CI [-8.5; 2.1] p= 0.04), and FEV1% of predicted (r=0.889, p<0.05).
Objective: To assess the appropriateness of antibiotic prescription in patients diagnosed with asthma exacerbations in the A&E department.

Method: All adult patients presenting at the A&E department over 10 consecutive months (January to October 2010) were included in a prospective study. Comparative statistical analysis was carried out using the t-test.

Results: A total of 244 patients were included. Forty-eight patients (19.7%) had been prescribed antibiotics by their general practitioner prior to presentation to A&E. Of 201 patients (82.4%) who had a radiological infiltrate suggestive of pneumonia, 12 patients (6%) had a white cell count (WCC) that was above normal levels. Antibiotics were prescribed in 65.9% of admitted patients. Of these patients 9.5% had a radiological pneumonia. Of 12 patients (8%) who had a raised WCC, 23% were febrile at presentation and 73% had symptoms of a respiratory tract infection. Antibiotics were prescribed to 39.7% of discharged patients.

Conclusion: There is a trend towards unnecessary antibiotic prescription in asthma exacerbations, with 39.7% of patients having evidence of radiological pneumonia or concomitant bacterial infection of the respiratory tract.