413. Asthma management and response

P3951

Effects of formoterol-budesonide combination on residual eosinophilic inflammation in distal airway of patients with well-controlled moderate asthma

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Aims: To investigate whether formoterol-budesonide combination (FBC, Symbicort TM) controls residual eosinophilic inflammation in the distal airways of well-controlled asthmatic patients more effectively than salmeterol-fluticasone propionate combination (SFC).

Methods: Twenty eight outpatients (58.4±19.7yrs) with well-controlled moderate asthma who had used SFC for more than 3 months were the subjects. Evidence of eosinophilic cationic protein (ECP) and surfactant protein D (SP-D) in 10% hypertonic saline-induced sputum was assessed, together with pulmonary fuction testing, impulse oscillometry system (IOS) and exhaled nitric oxide (FeNO).

Results: Eosinophilic inflammation was detected in the distal airway of eleven patients (39.3%) and they were switched to FBC (4,5/160ug, 2 inhalations twice daily). As higher levels of sputum SP-D were obtained from the nearer peripheral airway area, significantly higher ECP levels in late-phase sputum may indicate

residual asthmatic inflammation in the peripheral airway. The ECP levels in late-phase sputum) 255.2±297.1ug/1 at study entry) significantly decrease 60.0±43.7 (p=0.038) and 50.7±48.4 (p0.049) at 4 and 8 weeks after switching to treatment with the FBC, respectively. The FeNo levels (76.0±69.4 ppb at study entry) also significantly decreased 29.1±15.7 (p=0.017) at 8 weeks. The R5-R20 and AX values of IOS parameters also significantly improved after 8 weeks.
Conclusion: This study suggests that the FBC may give better control of residual eosinophilic inflammation in the distal airway compared to SFC therapy.

P3952
Montelukast as add-on therapy may improve some indices of small airways involvement in uncontrolled asthmatics
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Background: Several studies suggest an involvement of small airways in asthma that may contribute to poor disease control.
Aim: To assess whether montelukast improves indices of small airways involvement and clinical outcomes in asthmatics under regular therapy with medium-high doses of inhaled corticosteroids and long-acting β2-agonist.
Subjects and methods: 24 nonsmoker asthmatics underwent, at baseline and after one-month open label therapy with montelukast: FEV1, Single Breath Nitrogen Whashout for phase III slope (DN2); multiple flows exhaled nitric oxide (NO); eosinophils in sputum (Eo%); alveolar-arterial differences of respiratory gases (AaDO2, aADCO2); asthma control obtained by symptoms (S) and variability of peak expiration flow (ΔPEF) monitoring.
Results: Patients were divided in controlled (n=7 well controlled, n=10 partially controlled) and non-controlled (n=7), according to GINA guidelines. After one-month therapy with montelukast: a) in controlled group, therapy significantly reduced ΔPEF (18.2±9.1 vs 13.1±8.1, p=0.007); b) in non-controlled group, therapy significantly reduced only AaDO2 (32.1±7.9 vs 25.8±7.7 mmHg, p=0.034). Patients were also divided in other two groups according to the number of abnormal indices of small airways involvement (DN2, CaNO and AaDO2) at baseline: 0-1 vs 2-3 abnormalities. Montelukast reduced ΔPEF (21.8±7.8 vs 17.3±11.2, p=0.001) only in patients with 2-3 abnormalities in small airway indices.
Conclusions: Montelukast might improve both functional and clinical indices of small airways involvement, in controlled and non-controlled asthmatics and this might be associated with some effects on small airways.

P3953
The eXpeRience registry: Monitoring the "real-world" effectiveness of omalizumab in allergic asthma
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The observational, global eXpeRience registry was established to collect "real-world" data from omalizumab-treated allergic asthma patients. The registry aims to collect data on effectiveness/safety of omalizumab for up to 2 years during standard clinical practice.
This interim analysis included 876 patients (mean age, 44.9 years) with uncontrolled allergic (IgE-mediated) asthma receiving 8 months' omalizumab therapy.
At baseline, mean duration of allergic asthma: 19.5 (SD 13.74) years; mean total IgE serum levels: 316.6 (SD 419.13) IU/mL.
After 8 months, omalizumab effectively reduced asthma exacerbations/asthma-related healthcare utilization (Table). Moreover, OCS maintenance therapy was reduced or stopped in 55.6% patients compared with baseline. Overall, mean total AQLQ score improved by +1.04 (SD 1.34) and 58.2% patients had a clinically meaningful increase of ≥0.5. Asthma control also improved, with clinically relevant mean overall ACQ score change of -0.74 (SD 1.174).

	Baseline (12 months pre-treatment)	Post-omalizumab (after 8 months of treatment)
Exacerbations, mean (SD)		
Clinically significant*	4.8 (5.12)	0.4 (0.73)
Severe†	2.1 (2.67)	0.1 (0.37)
No. asthma-related, mean (SD)		
Medical healthcare uses‡	6.2 (7.08)	0.3 (0.91)
Missed work days	30.7 (58.45)	1.2 (7.43)
Missed school days	15.2 (24.36)	0.2 (1.26)

*Asthma worsening requiring rescue OCS; †clinically significant exacerbation defined as PEF reduction to <60% predicted; ‡calculated if all 3 parameters given (asthma related hospitalizations; emergency room visits; unscheduled doctor visits.)

Results demonstrate omalizumab's effectiveness in real-life clinical practice, further supporting efficacy of omalizumab shown in clinical trials.

P3954
Omalizumab and malignancy: Interim results from the EXCELS study
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Background: Omalizumab is a biologic for the treatment of moderate-to-severe persistent allergic asthma that is inadequately controlled with inhaled corticosteroids. At the time of FDA approval, the incidence of malignant neoplasms was higher among patients who had received omalizumab (0.5%) compared to placebo (0.2%) in clinical trials.
Objective: The EXCELS study is an FDA postmarketing commitment to evaluate the long-term safety of omalizumab.
Methods: EXCELS is an ongoing prospective observational study of approximately 5000 omalizumab-treated and 2500 non-omalizumab-treated moderate-to-severe persistent allergic asthma patients aged ≥12 years from 448 US centers who are followed for up to 5 years. All reported potential malignancies are reviewed by an independent oncology panel. The primary analysis includes confirmed, incident study-emergent primary malignancies.
Results: This analysis of malignancy rates was based on interim study report 6 (data through 11/30/2010) which comprises 18,860 person-years in the omalizumab cohort and 10,947 person-years in the non-omalizumab cohort. Both cohorts had an average follow-up of 3.8 person-years. The incidence of study-emergent primary malignancy was 12.78 and 14.48 per 1000 person-years in the omalizumab and the non-omalizumab cohorts, respectively, corresponding to a rate difference of -1.70 per 1000 person-years (95% CI: -6.43 to 2.21).
Conclusions: In this analysis, the incidence of malignancy was similar in the omalizumab and non-omalizumab cohorts. These interim results are preliminary and the study is still ongoing. Because the study is observational, selection and other biases cannot be excluded.
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P3955
Factors influencing the relative effect of leukotriene receptor antagonists (LTRA) and inhaled corticosteroids (ICS) as monotherapy in persistent asthma: A systematic review
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Objectives: To compare the safety and efficacy of LTRA with ICS in patients with asthma across age groups, over time, baseline severity and ICS dose.
Methods: In a systematic review until Dec 2010, we included randomised controlled trials comparing LTRA to ICS for ≥30 days in children and adults with asthma. The primary outcome was exacerbation requiring systemic steroids. Secondary outcomes included lung function, asthma control, adverse effects and withdrawals.
Results: The 54 included trials comprised 13,460 patients (2,795 children) with mild (42%) or moderate (58%) airway obstruction. In 84% of trials, LTRA was compared to a low ICS dose over 4-52 weeks. Compared to ICS, 48% more patients treated with LTRA suffered exacerbations requiring systemic steroids (RR 1.48; 95% CI 1.18, 1.85). There was no significant difference in the magnitude of effect between children and adults, ICS dose, and over time. The benefit of ICS over LTRA was greater in patients with moderate vs. mild airway obstruction (RR=2.03 vs. 1.25, p<0.01). FEV1, symptoms, night awakenings, rescue β2-agonist use, symptom-free days, and quality of life favoured ICS at almost points of time. LTRA use was associated with more than a 2-fold increased risk of withdrawals due to poor asthma control (RR 2.58; 95% CI 2.01, 3.30). Both options were equivalent in the risk of overall side effects.
Conclusions: ICS remains superior to LTRA to prevent exacerbations and improve asthma control, irrespective of age group, ICS dose, and duration of treatment. However, the benefit of ICS is significantly greater in patients with moderate airway obstruction.

P3956
Real-life effectiveness of beclomethasone diproprionate/formoterol extra-fine combination in adult patients with persistent asthma
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Background: Efficacy and safety of extra-fine beclomethasone dipropionate 100 μg/formoterol 6 μg pMDI (BDP/F) in adult patients with moderate-to-severe persistent asthma has been demonstrated in double-blind randomized controlled clinical trials.
Objective: To assess real-life effectiveness of BDP/F on asthma control.
Methods: Non-interventional, prospective, open-label, multicentre study in Bel-

gium from December 2008 till December 2010. Patients were enrolled by pneumologists and general practitioners (GPs). Visit 1 (Day 0): demographic and baseline asthma control data collection, initiation of BDP/F treatment; Visit 2 (Day 61-240) and Visit 3 (Day 241-420): evaluation of asthma control by patients (Juniper ACQ7) and investigators (GINA asthma control score), assessment of BDP/F safety/tolerability.
Results: 619 patients were enrolled: mean age 48±16.9 years, 54% female, 22.8% smokers, mean FEV_1% pred 78.6±20.0%. At visit 3 the mean daily beclomethasone dose was 266±127µg.

Table 1. Evolution of ACQ7 and GINA asthma control scores

	Visit 1	Visit 2	Visit 3
ACQ7 (mean ± SD)	2.24±1.13	1.05±0.82*	1.00±0.83*
GINA score improved (% patients)**		46.8	49.3
GINA score stable (% patients)**		44.6	41.7

*P<0.0001 vs Visit 1; **vs Visit 1.

Similar improvements in asthma control, evaluated as patient-reported ACQ7 score or physician-rated GINA asthma control score, were observed in patients recruited by pneumologists and by GPs. Treatment-related non-serious adverse drug reactions were reported in 16 patients (2.6%).
Conclusion: The results of this study demonstrate the real-life effectiveness of extrafine BDP/F in adult patients with moderate-to-severe persistent asthma.

P3957
Effect of budesonide/formoterol, budesonide and terbutaline on exercise-induced bronchoconstriction in mild intermittent asthma
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Objectives: To compare the protective effect over 6 weeks of budesonide/formoterol (B/F) as-needed, budesonide (B) once daily, and terbutaline (T) as-needed on exercise induced bronchoconstriction (EIB) in adults and adolescents.
Methods: Randomized, double-blind, double-dummy, multicenter, parallel group study (NCT00989833). Patients with EIB (fall in FEV_1 ≥10% from pre-exercise baseline) were treated with either B/F 160/4.5 mg prn, B 400 mg od + T 0.4 mg prn, or T 0.4 mg prn. All subjects should exercise 3-4 times/week and use B/F or T pre-exercise and for symptom relief during the study. The primary variable (max fall in FEV_1 post standardized exercise challenge + dry air inhalation) was investigated by covariance analysis. Symptoms from diary and ACQ were collected.
Results: 66 patients were randomized. Both B/F and B were superior to T in protecting against EIB. Mean reduction in post-exercise FEV_1 compared with baseline was 5.4% for B/F (p=0.017 vs T), 6.6% for B (p=0.0026 vs T) vs an enhanced bronchoconstriction of 1.5% for T. The effect of B/F and B did not differ significantly (p=0.58). Similar differences between groups were noted for area under the FEV_1 curve and average fall in FEV_1. No difference was observed between B/F, B and T in patient reported symptoms and ACQ. The mean total budesonide dose was higher in the B group (393mg) than in the B/F group (163 mg).
Conclusion: B/F before exercise and as needed is equally effective as regular once daily B in protection of EIB in patients with mild intermittent asthma and more effective than standard treatment with a short-acting beta-agonist used before exercise and as needed.
Sponsored by AstraZeneca.

P3958
Randomized, placebo-controlled study of asthmatic smokers treated with montelukast or mid-dose fluticasone
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Background: Previous data suggest smoking reduces therapeutic effectiveness in asthma, particularly for corticosteroids (CS) (*Lazarus et al. AJRCCM. 2007;175:783-90*). This study evaluates montelukast (Mont) 10mg daily and fluticasone propionate (FP) 250µg bid, each compared with placebo (Pbo), in patients with self-reported active smoking (after previous inability to quit) and asthma.
Methods: Patients (ages 18-55 years, with asthma [≥1 year], FEV_1 60%-90%predicted, airway reversibility [≥12%], and active smoking [≥0.5 to ≤2 packs/day]) were randomized (after a 3-week, single-blind, placebo run-in) to 1 of 3 parallel, 6-month, double-blind treatment arms. Primary efficacy endpoint was Percent of days with Asthma Control (%days-AC) during treatment; AC was defined as a composite: β-agonist (SABA) ≤2 puffs/day, no nighttime symptoms (N-Sxs), and no unscheduled healthcare (U-Hc) or systemic-CS use. Adverse events (AEs) were also evaluated.
Results: The%days-AC over 6 months of treatment was 45% (Mont [N=347]), 49% (FP [N=336]) and 39% (Pbo [N=336]); p-values for Mont and FP (each vs Pbo) were p<0.05 and p<0.001, respectively. The difference between Mont and FP was not significant (p=0.14). Components of%days-AC (SABA and N-Sxs) also showed significant differences from Pbo, but Asthma Attacks (defined as U-Hc or systemic-CS use) were infrequent and not significantly different. AEs occurred in similar proportions among treatment groups.
Conclusion: In a population of asthmatic patients actively smoking cigarettes, both montelukast 10mg daily and fluticasone 250µg bid significantly increased the percent of days with asthma control, compared with placebo.

P3959
'Real-life' persistence beyond the first year of omalizumab treatment in patients with severe allergic asthma: The R-Pixel study
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Background: Omalizumab (OMA) treatment has been shown to be effective in patients with severe allergic asthma (SAA), but published data beyond the first year of treatment are scarce.
Objectives: To examine the persistence rate (PR), to identify reasons for discontinuation and to determine the response rate (RR) and the clinical effectiveness beyond the first year of OMA treatment.
Methods: Of 105 patients who were on OMA treatment at the end of the 52w observational PERSIST study (Respir Med 2009; 103: 1633), 53 (51%) participated in this study. A retrospective medical chart analysis was performed at approx. 16, 52, and 68w after the end of the PERSIST study (up to 120w of treatment). Measurements included PR, physician-rated Global Evaluation of Treatment Effectiveness (GETE), Asthma-related Quality of Life Questionnaire (AQLQ), and systemic glucocorticosteroid (sGCS) use, emergency room (ER) visits and hospitalizations for severe exacerbations.
Results: The PR at 120w was 84.9%. Treatment was discontinued in 3 cases by patient decision (1 relocation, 1 AE, 1 non-compliance with office visits), in 3 patients by joint patient/physician decision (2 complete asthma control, 1 AE) and in 2 patients due to non-OMA related death. Where data were available, RR (good+excellent GETE) was >85%. Absolute change of ≥0.5 point in AQLQ score remained >90% from 0w up to 120w; less than 18.9% of patients required sGCS, there were no ER visits and only 1 hospitalization during the evaluation period.
Conclusions: These preliminary results indicate a high PR with OMA beyond the first year of treatment under "real-life" conditions in SAA patients in Belgium.

P3960
Plasma and urinary concentrations of inhaled salmeterol in healthy and persons with asthma – Quantifying a doping limit
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Background: Salmeterol is a long acting β2agonist that is used in treatment of asthma. β2agonists are on WADA and IOC's prohibited list, but salmeterol is allowed in therapeutic doses by inhalation. The prohibited list however contains no urinary limit for salmeterol, which gives athletes the opportunity to inhale unlimited doses of salmeterol. Large doses of β2agonists may have ergogenic effects and therefore a quantification of a urine salmeterol limit is necessary.
Purpose: To find plasma and urinary concentrations of inhaled salmeterol by inhalation in therapeutic dose 100 µg in healthy and persons with asthma. To discuss a urinary concentration limit for inhaled salmeterol on the prohibited list.
Methods: 10 persons with asthma (A) and 10 healthy subjects (C) were enrolled, age 24.6±3.9. The subjects underwent two visits. First visit was a pre-examination with a metacholine provocation and lung function test. On second visit the subjects inhaled 100 µg salmeterol (Serevent©) as a single dose. Blood samples were acquired at baseline and 0.5, 1, 2, 3, 4 and 6 hours after administration. Urinary samples were collected at baseline and 4, 8 and 12 hours after administration. Plasma and urine samples were analyzed by liquid chromatography mass spectrometry.

Results: The peak median urinary concentration was found after 4hrs reaching 0.38±0.26 ng mL^{-1} in A and 0.38±0.22 ng mL^{-1} in C. Peak median plasma concentration was 0.07±0.03 ng mL^{-1} for A and 0.06±0.03 ng mL^{-1} in C. No differences were found between the groups.
Conclusions: Urine salmeterol peak 4h after administration by inhalation. We propose a salmeterol urine limit of 0.82 ng mL^{-1} in doping controls.

P3961
The effect of liposome inhalation on non-invasive oxidative stress markers in patients with bronchial asthma
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Background: The liposome inhalation demonstrates an antioxidant activity in the treatment of various diseases, confirmed both by experimental and clinical studies. The aim is to carry out a prospective study of antioxidant features of liposome admission in patients with the exacerbation of bronchial asthma.
Materials and methods: We enrolled 50 patients (age=37±7.5 year, men=64%) with mild-to-moderate bronchial asthma (FEV1>70%, steroid-naive) in prospective comparison study. All patients were divided in two groups: group 1 contains 25 patients, who received a liposome inhalation by compression nebulizer once a day (300 mg of phospholipids in each admission); group 2 contains 25 patients, who received a traditional therapy (control). Antioxidant activity was determined by the estimation of the exhaled nitric oxide level (ENO) and total nitrite/nitrate (TNN) in exhaled breath condensate before and after the investigation period.
Results: There was a significant decrease of ENO level in group 1 from 31.8±2.4 to 7.1±1.4 ppb ($p<0.001$) after the observing period. In group 2 the ENO level was decreased from 29.7±3.9 ppb to 25.0±2.5 ppb (not significant). Patients in both groups had significantly higher levels of TNN before the study (7.9±0.9 μ M and 8.4±1.1μM respetively). After liposome admission the TNN level in group 1 decreased to 0.9±0.1 μ M ($p<0.01$) as well as in control group it was at the same border (7.7±1.4 μM).
Conclusion: The results obtained demonstrate that liposome inhalation administered once a day during 14-days period has a significant antioxidant effect in patients with mild-to-moderate bronchial asthma.

P3962
Quantitative IgE levels in asthma and implications for treatment with omalizumab. Are the cutoffs to narrow?
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The use of omalizumab is constrained by the narrow quantitative parameters in its use. This study looks at experience in a small pulmonary practice as regards to treatment with omalizumab outside the usual boxed "guideline" quantitative parameter.
Patients (n=132) with asthma who were treated with omalizumab but had IgE levels less than (<)30 iu/ml or greater than (>)700 iu/ml which is considered to be "guideline" quantitative values were asked to complete a questionnaire from which satisfaction (1-5) and symptom scores (1-4) were extracted. We looked for a difference in scores when compared to the usual guideline group (IgE levels 30-700 iu/ml) in a small practice.
There was no significant difference between symptom and satisfaction scores for patients with IgE <30 iu/ml and IgE >700 iu/ml in the usual guideline group. Symptom scores for <30 iu/ml were p=0.301078 and >700 iu/ml were p=0.517811. Satisfaction scores for IgE <30 iu/ml were p=0.774777 and >700 iu/ml were p=0.987994031. Difference in symptom scores for <30 iu/ml and 30-700 iu/ml were 0.162617. Difference in symptom scores for >700 iu/ml and 30-700 iu/ml were 0.105474. Difference in satisfaction scores for <30 iu/ml and 30-700 iu/ml were 0.08972. Difference in satisfaction scores for >700 iu/ml and 30-700 iu/ml were 0.004006.
There is need for randomized controlled studies to address the issue of outside the quantitative box levels of IgE given the vast spectrum of IgE levels in patients with asthma. On a case by case basis where patients fall outside the quantitative guidelines, omalizumab may enhance treatment options and improve outcomes in patients with asthma.

P3963
The effect of statin usage on airway inflammatiory cells and markers, and clinical indices in asthmatic patients
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Introduction: Asthma has been characterized with airway inflammation. Statins have immunomodulatory properties in addition to lowering cholesterol. However their effects in asthmatic patients have not been evaluated yet.
Aim: To define the effect of statins on inflammatory markers, cells and clinical indices in asthmatics.
Method: 51 patients with asthma were included in the study. Pulmonary function tests (PFT), metacholine bronchoprovocation test, peripheral blood smear, blood total IgE value, IgE specific sub-groups were evaluated during the initial evaluation. After taking asthma questionnaires, ACQ and AQLQ, induced sputum samples were collected. Cells were counted in the induced sputum and the supernatant was evaluated for IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-alfa and VEGF levels with ELISA in all patients at the baseline. 25 asthmatic patients with LDL >130mg/dl were treated with Rosuvastatin at the following 8 weeks, then all patients were re-evaluated with the same studies.
Results: 8 week treatment with Rosuvastatin resulted in improvement of MEF (L/s) ($p<0,005$), MEF (% pred.) ($p<0,0001$) and FEV1/FVC (%) ($p<0,0001$). Peripheral eosinophilia ratio (from 3.7±1.2% to 2.2±1.1%) ($p<0,05$), TNF-alfa (from 0.91±1.1 to 0.22±0.7 pg/ml) ($p<0.0001$) and IL-6 (from 18.7±23.4 pg/ml to 9.9±37.2 pg/ml) ($p<0.0001$) levels decreased. However the questionnaire results did not change. Controls did not have any improvements in the evaluated parameters.
Conclusion: We conclude that statins suppress inflammatory and allergic markers and improve PFT in asthmatic patients. This may be an opportunity to develop a new treatment for asthmatic patients.

P3964
Stability and achievement of asthma control with higher doses of inhaled conticosteroids regular treatment
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Background/purpose: Uncontrolled asthma is characterized by variability. Previous GOAL study demonstrated that once asthma is achieved, the future risk of instability is greatly reduced. Higher stability (lower variability) in asthma control is also associated with a lower future possibility of unscheduled healthcare resource use. In the study, we attempted to increase inhaled combined agent doses initially and hypothesized that stability was positively associated with the level of control achieved.
Methods: This was a prospective study and new diagnosed asthma patients were included and randomized into two groups. One group was treated with higher doses (HD) one month then shifted to guideline-practice (GP) treatment and another was treated with GP therapy model. Peak expiratory flow (PEF), asthma control test (ACT) and exacerbation times were measured. The follow-up time was 1/2 year.
Results: 39 patients were treated with HD and 40 patients were GP therapy policy. PEF change were significantly improved in HD group compared with GP (56±17 vs. 45±19, p=0.04). The obvious improvement especially in initial 2 months (77±39 vs. 52±23, p=0.01). There were significantly differences in ACT change and exacerbation frequency in patients with mild and moderate persistent asthma using HD therapy.
Conclusion: Our findings demonstrated that patients with HD treatment were more improved and stabilized than patients with previous conventional therapy policy. Further evaluation should be performed more patients and long term follow-up to confirm the higher doses' efficiency.

P3965
Comparison of the efficacy of cicleosonide with budesonide in mild to moderate asthma patients after step-down therapy
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Inhaled corticosteroids are the most widely used controller treatment for asthma, and is the stepping down level when asthma is controlled with combination therapy. Ciclesonide is an inhaled corticosteroid with on-site lung activation that provides anti-inflammatory activity. The aim of this study was to compare the efficacy of ciclesonide (CIC) with budesonide (BUD) in 142 adult patients with mild to moderate asthma who were well-controlled with a combination of inhaled corticosteroids and long-acting b2-agonist. They were randomized to receive once-daily ciclesonide 320mg (n=73) or twice-daily 2 inhalations of budesonide 200 mg (n=69) for 12 weeks. The forced expiratory volume in one second (FEV1), maximum mid-expiratory flow (MMEF) and asthma control test (ACT) score were evaluated. Tolerability and ranked stratification of patient and physician were assessed. At the end of study, the withdrawal rate of CIC group (26.4%) was significantly less than that of BUD group (42.7%, p=0.02). There was no difference of FEV1 and MMEF throughout 12-week treatment period in CIC group. In BUD group, FEV1 decreased significantly at 4-week (1.8±0.1 L, n=59, p=0.0006) and 12-week of treatment (1.9±0.1 L, n=39, p=0.01) compared with baseline (2.0±0.1 L, n=69). MMEF decreased significantly at 4-, 8- and 12-week compared to baseline in BUD group. ACT score decreased significantly at 4-week of treatment in BUD group compared with baseline,. There was no difference of ACT score over the 12-week period in CIC group. In conclusion, cicleosonide was more effective and better drug adherence than budesonide in the stepping-down treatment of asthma from combination therapy.

P3966

The effect of GSK2190915, a 5-lipoxygenase activating protein inhibitor, on the early asthmatic response to inhaled allergen

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Background: GSK2190915 is a potent 5-lipoxygenase activating protein inhibitor, thereby inhibiting the synthesis of leukotrienes and 5-oxo-ETE.
Objective: To assess the effects of GSK2190915 on the allergen induced early asthmatic response (EAR).
Methods: 19 patients with mild asthma were enrolled in this 3-centre, double-blind, 3-way crossover study. They took 10 and 50 mg GSK2190915 and placebo orally, once daily for 3 days, in randomised order. On Day 3 they had an inhaled allergen challenge.
Results: GSK2190915 had a significant effect on the EAR, the treatment difference from placebo for 10 mg was 0.212 L (0.044, 0.379) and for 50 mg was 0.409 L (0.242, 0.576) for minimum FEV_1 in the 2 hours after allergen inhalation. The magnitude of the effect with 50 mg GSK2190915 in this study was comparable to that observed with 100 mg on the EAR in a separate study [1]. Safety and tolerability were good.

Endpoint	Placebo (N=17)	GSK2190915	
		10 mg (N=18)	50 mg (N=19)
Mean minimum FEV1 absolute change from baseline (0–2h), L (95% CI)	–1.137 (–1.380, –0.894)	–0.925 (–1.166, –0.685)	–0.728 (–0.966, –0.490)
Mean weighted mean FEV1 absolute change from baseline (0–2h), L (95% CI)	–0.540 (–0.710, –0.369)	–0.423 (–0.592, –0.255)	–0.236 (–0.403, –0.070)
Mean % attenuation of the placebo response to allergen minimum FEV1 (0–2h)		18.6	36.0
Mean % attenuation of the placebo response to allergen weighted mean FEV1 (0–2h)		21.5	56.2

Conclusion: GSK2190915 has shown a significant, dose related, inhibition of the EAR to inhaled allergen.
References:
[1] V Norris et al. ERS conference 2011.
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P3967

Asthma control and lung function after step down from high dose ICS/LABA combination therapy

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Rationale: Guidelines recommend asthma treatment to be adjusted to the lowest dose maintaining control.
Objectives: To evaluate whether lung function and asthma control can be maintained in patients treated with high dose ICS/LABA combination after step-down.
Methods: Prospective, multinational, randomized, open label, parallel group controlled trial. Patients treated with high dose (1000/100 μg daily) fluticasone/salmeterol (FP/S) either DPI or pMDI entered a 2-month run-in with FP/S Diskus 1000/100 μg daily. Controlled patients (GINA) were treated with either FP/S Diskus 500/100 μg daily or extrafine beclomethasone/formoterol (BDP/F) pMDI 400/24 μg daily for 6 months. Morning PEF was the primary outcome. Secondary outcomes included asthma control.
Results: 378 patients were evaluated for ITT; previous treatment was DPI in 87% of patients. Equivalence was shown in morning PEF at the end of treatment (difference between means 2.49 L/min; 95% CI -13.43 to 18.42).
Morning PEF remained above 95% predicted throughout the study, though absolute values decreased (414.4 to 397.1 L/min for BDP/F; 429.7 to 394.6 L/min for FP/S; p=0.0001). Asthma control was maintained in the majority of patients with no worsening in FEV_1 measured at clinics, symptoms score, use of rescue medication and no differences in any parameter including exacerbations.
Conclusions: Patients controlled with high dose ICS/LABA DPI can be stepped-down to medium dose either DPI or extrafine pMDI mantaining asthma control.

Parameter	BDP/F (n=187)	FP/S (n=191)	Between groups p value
Controlled, % pts	89.7	84.0	0.291
Partly controlled, % pts	6.7	9.7	0.291
Uncontrolled, % pts	3.6	6.3	0.291
Severe exacerbations, % pts	2.1	2.7	1.000

P3968

Risks of diabetes mellitus and hyperglycaemic adverse events in patients with asthma taking inhaled corticosteroids

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Background: A recent study of patients with lung disease and with prescriptions for inhaled corticosteroids (ICS) detected a 34% increased risk of diabetes mellitus.
Methods: A retrospective analysis evaluated the double-blind, placebo-controlled, clinical trials in asthma (duration >3 months) in patients ≥4 years of age, involving budesonide (BUD) or BUD/formoterol (26 trials, n=9067 for BUD; n=5926 for placebo). A supplementary dataset evaluated all double-blind, non-placebo controlled trials in asthma (duration >3 months), involving the use of ICS (60 trials, n=33496 for BUD, n=2773 for fluticasone propionate [FP]). Cox proportional hazards regression modelling, both adjusted and not adjusted by study, was used to estimate the relative effect of ICS on diabetes mellitus/hyperglycaemia adverse events (AEs) or serious adverse events (SAEs) in both the primary and supplementary datasets.
Results: In the primary dataset, the occurrence of diabetes mellitus/hyperglycaemia AEs was 0.13% for BUD and 0.13% for placebo (HR 0.98 [95% CI: 0.38–2.50], p=0.96); the occurrence of diabetes mellitus/hyperglycaemia SAEs was 0% for BUD and 0.05% for placebo. In the supplementary dataset, the occurrence of diabetes/hyperglycaemia as AE and SAE was 0.19% and 0.03%, respectively. There was no increased risk with higher doses of BUD, nor any difference between BUD and FP. The risk for diabetes mellitus/hyperglycaemia increased with age, BMI and disease severity.
Conclusion: This retrospective analysis of all double-blind trials with BUD in asthmatic patients did not demonstrate any increased risk of diabetes mellitus/hyperglycaemia with BUD treatment.
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P3969

Increased incidence of pulmonary embolism in severe asthma

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Introduction: Many patients with severe asthma need inhaled (ICS) and chronic oral (OCS) corticosteroids for asthma control. OCS are associated with hypercoagulability and increased risk of venous thromboembolism (VTE). Also asthma itself is associated with a prothrombotic state (Brims 2009).
Hypothesis: The incidence of VTE is increased in asthma, and associated with asthma severity and OCS use.
Methods: 166 Outpatients with mild-moderate asthma (mean (range) age 49yr (18-80), 56% female, all using ICS), and 139 patients with severe asthma (52yr (18-77), 62% female, 39% using OCS) from 3 clinics in the Netherlands and Davos, Switzerland, were consecutively included in a cross-sectional study. Patients completed a questionnaire about previous VTE, risk factors and medication use. All VTE events were objectively diagnosed. Data were compared with the available incidence (ages 50-54 yr) in the general population (Naess 2007).
Results: Deep vein thrombosis (DVT) occurred in 3 and 2 patients with severe and mild-moderate asthma resp. and pulmonary embolism (PE) in 11 and 3. Overall incidence was 1.77/1000 person yr in severe asthma *vs* 0.7 in mild-moderate asthma and 1.03 in the general population. The relative risk of PE for severe asthma was 5.5 (95% CI: 1.24-24) and independently associated with >2 exacerbations/yr (RR 12.63, 1.48-107) and chronic OCS use (RR 8.21, 1.57-43). The risk of DVT was 0.50 (0.13-1.96). In mild-moderate asthma risks were not increased.
Conclusions: Patients with severe asthma have a 5.5-fold increased incidence of pulmonary embolism, which is associated with exacerbation frequency and chronic oral corticosteroid use.
Implication: Pulmonary embolism may be important in the prognosis and management of severe asthma.

P3970

Effects of hydrocortisone on acute beta-blocker and histamine induced bronchoconstriction

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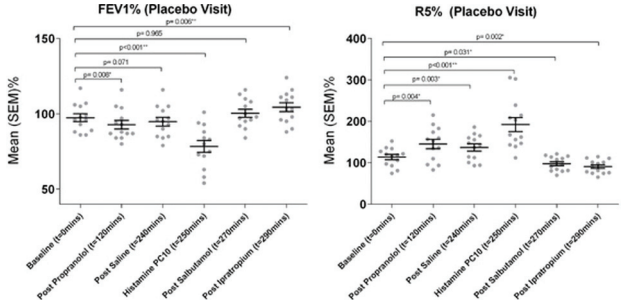
Introduction and objectives: The benefits of chronic beta-blockade in asthma have recently been questioned, however concerns of bronchoconstriction persist with the greatest risk after first dose. We investigated the safety of acute exposure to propranolol in asthmatics, sequentially challenged with histamine to mimic an asthma exacerbation and evaluated the role of hydrocortisone in potentiating salbutamol reversibility.

Methods: Persistent atopic asthmatics, $\leq$1000μg/day budesonide performed a randomised double-blind placebo-controlled crossover study. Following 10mg or 20mg of oral propranolol, patients received 400mg iv. hydrocortisone or placebo, followed by histamine challenge with nebulised salbutamol 5mg and ipratropium 500mcg recovery.

Results: 13 patients completed per protocol. Hydrocortisone did not potentiate salbutamol recovery post-propranolol and histamine challenge. Beta-blocker induced bronchoconstriction was demonstrated by spiromery and IOS. For the placebo visit, FEV_1% fell 4.7% 2hrs post-propranolol whilst R5% increased 31.3%. On both visits FEV_1% and R5% returned to baseline after salbutamol post-histamine.



Conclusion: Nebulised salbutamol produced a full recovery after propranolol and histamine induced bronchoconstriction, independent of hydrocortisone use. Our findings offer reassurance to those undertaking further evaluation of chronic beta-blockade as a potential treatment for asthma.