257. Clinical aspects and treatment of asthma and allergic respiratory diseases

P2338
The APEX study: A retrospective review of outcomes in patients with severe allergic asthma who were or were not hospitalised in the year prior to omalizumab initiation in UK clinical practice
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The link between increasingly severe asthma and increased hospitalisation risk is well established. We retrospectively reviewed medical records 12 months pre- and post-omalizumab initiation in patients (≥12 years) with severe persistent allergic asthma who were (n=81) or were not (n=55) hospitalised for asthma in the year before omalizumab initiation. Baseline characteristics in hospitalised and non-hospitalised patients were similar: mean age 39.7 and 43.6 years; 27.2% and 38.2% male; mean IgE 278 and 309 IU/mL, respectively. Post-omalizumab initiation there were significant improvements in oral corticosteroid (OCS) burden (primary endpoint), % patients stopping OCS, exacerbation rates and Asthma Quality of Life Questionnaire (AQLQ) scores. Overall, similar benefits were seen regardless of hospitalisation in the previous year. This suggests that prior hospitalisation is not a good predictive discriminator of response to omalizumab in patients with severe allergic asthma.

P2339
Effectiveness of omalizumab in improving quality of life in patients with ’steroid-resistant’ asthma and severe allergic rhinitis
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Asthma is a heterogeneous disease, not only in its clinical expression and course but also in its response to treatment with deleterious effects on Quality of life (QoL). Anti-IgE can spare these patients with unnecessary exacerbations and have a better QoL. The objective of this study was to evaluate the effectiveness of omalizumab treatment in improving QoL in patients with severe allergic rhinitis and asthma.

Methods: 41 patients aged ≥18 years with steroid-resistant asthma were enrolled in this open label study. Patients were examined at baseline and were treated with omalizumab administered subcutaneously every 2 or 4 weeks (at least 0.016 mg/kg/IgE IU/mL), in addition to existing treatment. At both visits, investigators assessed QoL on a 4 point scale in the following domains: nasal, ocular and asthmatic symptoms. Scores were calculated for individual symptoms, total scores for each domain. Patients were also assessed on impairment of sleep and daily activities.

Results: Omalizumab significantly reduced scores from baseline in both nasal and ocular symptoms. Reductions were also seen in the asthmatic symptom scores: significance was noted in wheezing (P=0.0002) and breathless scores (P=0.0002). At baseline, 62% of patients had some degree of daily activity impairment, whereas at the final visit only 31% had daily activity impairment. Similarly, while 55% of patients had some sleep impairment at baseline, this was reduced to 28% at the final visit.

Conclusions: This open label study demonstrated that omalizumab was an effective treatment for the symptoms and sleep/daily life impairments associated with severe allergic rhinitis and asthma.

P2340
Population pharmacokinetics of tralokinumab, an investigational anti-IL-13 monoclonal antibody, in asthmatic and healthy adults
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Interleukin-13 (IL-13) is considered a critical mediator in the development and maintenance of asthma. Tralokinumab (CAT-354), a human IgG4 monoclonal antibody that specifically neutralizes IL-13, is currently trialled in subjects with uncontrolled, severe asthma.

The aim of this study was to develop and evaluate a population pharmacokinetic (PK) model of tralokinumab. Four phase 1 studies and one phase 2a study constitute the data to be analysed comprising a population of 247 healthy and asthmatic adults. Nonlinear mixed-effects modeling of pooled data was conducted using the software NONMEM7. The influence of demographic features on tralokinumab PK was evaluated by covariate analysis. Predictive performance of the model was assessed through simulations. The PK parameters for a 2-compartment model after IV and SC dosing were all precisely estimated (RSE<26%) with mean values (CV% of between-subject variability) of clearance (CL), central volume (Vc), inter-compartment clearance (Q), and peripheral volume (Vp) respectively equal to 0.22 L day-1 (33%), 2 L (64%), 3.4 L (28%), and 1.4 L day-1 (64%). Body weight explained a minor portion of the variability in CL and Vp, 11% and 34% respectively. No PK difference was detected between healthy and asthmatic subjects. SC bioavailability was estimated at 82%. Model appropriateness was demonstrated by good predictive behaviours of the model. The population PK model successfully described the concentration time-course of tralokinumab and adequately predicted the variability in the studied population. It therefore constitutes a useful tool for guiding the design and dosing of tralokinumab in future clinical trials.

P2341
Cough variant asthma may be a incipience of bronchial asthma
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Cough variant asthma (CVA) is characterized by chronic cough that persists for more than two months and suggested to be a precursor of bronchial asthma (BA).

To analyze if the position of cough variant asthma is early or mild stage of the classical bronchial asthma analyzed according to the airway inflammation,
bronchial hypersensitivity, airway obstructive damage, newly diagnosed 46 cough variant asthma patients and 57 bronchial asthma patients naive to oral or inhaled corticosteroids and free of asthma exacerbation were subjected to spirometry, impulse oscillometry (IOS), bronchial hyperresponsiveness (BHR), induction of sputum, and measurement of fractional exhaled nitric oxide (FeNO).

Spirometry revealed lower values of FEV1.0/FVC, FEV1.0/FFS, and V25%pred in patients with BA than in those with CV A (p < 0.01). Both IOS parameters and FeNO values were significantly higher in patients with BA than in those with CV A (p < 0.01). The log PC20 was significantly lower in patients with BA than in those with CV A (p < 0.05). Induced sputum eosinophil counts were significantly higher in patients with BA than in those with CV A for both central and peripheral airways (p < 0.001). However, the values of IOS, PC20, FeNO, and induced sputum eosinophil counts did not differ significantly between patients with mild intermittent asthma and those with CV A.

All measures of central and peripheral airway obstruction, eosinophilic inflammation, and airway hyperresponsiveness were milder in patients with CV A than in those with BA, but the differences were not statistically significant.

**Aims and objectives:** The aim of the study was to compare the effects of budesonide/formoterol versus budesonide on airway dimensions and inflammation in asthma.

**Methods:** Fifty asthmatic patients were randomized to treatment with budesonide/formoterol or budesonide for 140 days. The percentage of eosinophils in induced sputum, pulmonary function, and Asthma Quality of Life Questionnaire (AQLQ) were also evaluated.

**Results:** Significant decreases were observed in WA/BBSA (p < 0.05), WA% (p < 0.001) and V4% BSA (p < 0.05), and increases in AI/BBSA (p < 0.05), and improvements in the AQLQ. These effects were observed in patients treated with budesonide/formoterol compared with budesonide. The reduction in sputum eosinophils and increase in FEV1% were greater for budesonide/formoterol compared with budesonide. The changes in WA were significantly correlated with changes in sputum eosinophil and FEV1% (r = 0.84 and r = 0.64).

**Conclusions:** Budesonide/formoterol combination is more effective than budesonide for reducing airway wall thickness and inflammation in asthma.

**P3243**

**Effects of breast feeding on the prevalence rates of asthma, rhinitis and eczema in Chinese school children**

Ning Song, Mohammed Shamsuin, Jin Zhang, Shuting Hao, Jianling Wu, Chunling Fu, Xixin Yan

**Background:** The combination of inhaled corticosteroids and long-acting β2-agonists results in improved asthma symptom control compared with inhaled corticosteroids alone, but the effects of combination therapy on airway structural changes are still unknown.

**Aims and objectives:** The aim of the study was to compare the effects of budesonide/formoterol versus budesonide on airway dimensions and inflammation in asthma.

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Ning Song, Mohammed Shamsuin, Jin Zhang, Shuting Hao, Jianling Wu, Chunling Fu, Xixin Yan

**Background:** Breastfeeding for at least 12 months is recommended by many governments and allergy organizations to prevent allergic disease. There is conflicting evidence concerning the relationship between breast feeding and asthma, wheezeing illness and allergic disorders. The objective of this study was to investigate whether there is any association between breast feeding and asthma and allergic disorders in Chinese schoolchildren.

**Methods:** Study subjects comprised 10824 randomly selected 6 to 18 year-old schoolchildren from Shijiazhuang in Hebei Province in China. Information on breast feeding, asthma, rhinitis and eczema was gathered by parental questionnaire using the Chinese version of ISAAC questionnaire.

**Results:** Children who have been breastfed had significantly lower prevalence rates of exercise-induced wheezeing, asthma ever, and rhinitis ever than those who have not been breastfed (3.1% vs 4.2%; P < 0.05; 1.0% vs 1.6%; P < 0.05; and 13.3% vs 15.8%; P < 0.01; respectively). There was a similar trend with chronic rash ever. Children who have been breastfed more than or equal to 12 months had lower prevalence rates of ever wheezing, wheeze in the past year, exercise-induced wheezing, persistent cough past year, ever had rhinitis, and ever had eczema than those who have been breastfed less than 12 months (5.3% vs 6.8%; P < 0.05; 1.6% vs 2.7%; P < 0.05; 2.9% vs 3.9%; P < 0.05; 10.7% vs 12.4%; P < 0.05; 12.5% vs 16.2%; P < 0.001 and 11.4% vs 13.2%; P < 0.05, respectively). The present study confirms the protective effect of breastfeeding on symptoms of asthma, rhinitis and eczema.

**P3244**

**Effects of water aerosol on pediatric allergic asthma**

Christine Rolland, Michèle Lheritier-Barrand, Lisa Tauleigne, Marie David, Lise Lemenonnier, Erika Valovarta

**Background:** Water aerosols are known for reducing airway wall thickness and inflammation in asthma.

**Methods:** F Fifty asthmatic patients were randomized to treatment with budesonide/formoterol versus budesonide on airway dimensions and inflammation in asthma.

**Results:** Significant decreases were observed in WA/BBSA (p < 0.05), WA% (p < 0.001) and V4% BSA (p < 0.05), and increases in AI/BBSA (p < 0.05), and improvements in the AQLQ. These effects were observed in patients treated with budesonide/formoterol compared with budesonide. The reduction in sputum eosinophils and increase in FEV1% were greater for budesonide/formoterol compared with budesonide. The changes in WA were significantly correlated with changes in sputum eosinophil and FEV1% (r = 0.84 and r = 0.64).

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**P3244**

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**P3245**

**Simultaneous analysis of clinical markers for predicting increased lung function fluctuability in stable asthma**

Kazunto Matsunaga, Atsushi Hayata, Tsunahiko Hirano, Masakazu Ichinose

**Background:** Airway hypersensitivity (AHR) has been shown to be associated with the loss of asthma control. Predicting the increased fluctuation of lung function might be useful to regulate the future risk of poor asthma control because peak expiratory flow (PEF) variability well correlates with AHR.

**Objective:** We simultaneously analyzed the clinical markers for predicting increased PEF variability in stable asthma.

**Methods:** We studied non-smoking asthmatic patients who were receiving conventional therapy and clinically stable for 8 weeks. Patient medical records were obtained and asthma control questionnaire (ACQ), spirometry, and exhaled nitric oxide fraction (FENO) were measured. Associations between these variables and PEF variability over a week (Min%Max) were prospectively assessed.

**Results:** 52 of 287 asthmatics (17.5%) showed the increased PEF variability (Min%Max < 80%). These subjects were receiving more intensive therapy, but had more severe asthma symptoms, more airflow obstruction, and more evidence of airway inflammation. In fact, AHR, FENO, and expiratory volume in one second (% of predicted %FVEF1), and FENO were identified to be independent predictors of Min%Max < 80%. When we combine baseline %FVEF1 ≤ 85% and/or FENO ≥ 40 ppb, this index was associated with the highest combination of sensitivity (94.2%) and specificity (80.4%) for increased PEF variability.

**Conclusions:** These results suggested that AHR, %FVEF1 and FENO can stratify risk for increased fluctuation of lung function among the clinically stable asthmatics.

**P3246**

**Impact of allergy diagnosis on patients’ perceptions and experience of HDM allergy: A European survey**

Christine Rolland, Michèle Lheritier-Barrand, Lisa Tauleigne, Marie David, Lise Lemenonnier, Erika Valovarta

**Background:** We assessed allergy awareness and diagnosis in a survey in four European countries. A postal survey was distributed to determine the impact of diagnostic status on the perception of house dust mite (HDM) allergy and its management.

**Methods:** 4016 adults (France: n=1001; Germany: n=1002; Italy: n=1004; Spain: n=1009) answered an anonymous online, questionnaire on their perception and personal experience of HDM allergy. The results were analyzed according to whether the subjects had been diagnosed with HDM allergy by a physician (n=611) or not. Survey procedures complied with the ESOMAR International Code of Marketing and Social Research Practice.

**Results:** 56% of the overall survey population stated that they experienced symp-
P2347
Helmints for asthma: Findings of a Cochrane systematic review
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Background: Helminths modulate the natural immune response of their human hosts, and may prevent or cure immune-mediated or allergic diseases, such as asthma. Recent animal and humanised studies support this hypothesis.

Objectives: To assess the safety and effectiveness of helminth therapy in people with asthma.

Methods: We searched the Cochrane Airways Group Specialised Trials Register and other additional sources for published and unpublished trials. We included all randomised controlled trials where the intervention was any helminth species administered to people with asthma. We combined dichotomous data using risk ratio (RR) and continuous data using mean difference (MD).

Results: We found 5 published reports, describing 2 studies (64 adult participants). Both studies used a single percutaneous application of 10 third stage Necator americanus larvae. Pooling of data showed no difference in airway responsiveness between the helminth and placebo groups (MD 0.51, 95% CI –0.54 to 1.56) and no difference in study dropouts (OR 2.15, 95% CI 0.36 to 12.76). Other outcomes (asthma symptoms, use of reliever inhalers, quality of life) did not differ between the groups. Adverse events were few.

Conclusions: There was no clinical benefit from helminth therapy. The trials however were small and not powered to show effectiveness. Administered to humans in carefully measured doses, helminths appear to be safe. More preclinical studies should be performed, before larger and extended duration trials of helminths for asthma are carried out. ‘Trickle colonisation’ with helminths may be more effective. A larger clinical trial of helminth bolus, but this therapeutic approach has not yet been tested for asthma.

P2348
Changes in total and specific IgE following treatment with mebendazole in patients with persistent asthma and IgE to Ascaris lumbricoides
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Background: Recent studies have reported that patients with ascarisial and high IgE levels may suffer from asthma. This study aims at evaluating the changes in total and Ascaris-specific IgE, as well as in symptoms, following anti-helminthic therapy in patients with asthma not controlled with standard drug treatment.

Methods: 30 adult patients with persistent asthma and high levels of total and Ascaris-specific IgE were included in the study. Though they had been treated by associations of ibuprofen and corticosteroids (ICS) and long-acting beta-agonists (LABA), they shared irregular and unjustified asthma attacks and therefore referred to us in order to have a further check-up. They underwent spirometry, skin prick tests, total and specific IgE (Euroimmun and A. lumbricoides). To all patients a treatment by mebendazole 100 mg b.i.d for 3 days, based on two courses with a 20-day interval, was proposed. After 6 and 12 months, in case of persistent positivity, 2 other courses of mebendazole were prescribed.

Results: 24 patients underwent the treatment. The mean value of total IgE increased in 6 months of treatment from 1556 to 2206 but decreased after 12 months to 1352 kU/L. Similarly, specific IgE increased from 3.1 to 4.5 after 6 months and decreased to 2.4 kU/L after 12 months. Spirometry showed a basal FEV1 mean value of 59% and a rise to 71% after 6 months and to 78% after 12 months.

Conclusion: These findings confirm the association between Ascaris infestation and allergy-like symptoms and demonstrate that antiparasitic therapy remarkably reduces asthma attacks in patients who show high levels of total and specific IgE for A. lumbricoides.
Efficacy and safety of 300IR 5-grass pollen sublingual tablet in allergic patients with and without asthma. Robert K. Zeldin, Armelle Montagut, Jocisine Cognet-Sicé, Kathy Abiteboul. Global Clinical Development, Stallergenes S.A., Antony, France

**Background:** Efficacy and safety of 300IR tablet has been demonstrated. Here we report on efficacy and safety.

**Methods:** Grass pollen allergic adults were randomised to placebo or 300IR pre- and co-seasonally for 3 seasons, starting 4 months (4M) or 2 months (2M) prior to each season and continuing for its duration. Asthmatic patients requiring no more than GINA Step 1 therapy could be included. The primary efficacy endpoint, Average Adjusted Symptom Score (AASS), adjusting rhinoconjunctivitis symptoms for rescue medication use, scale 0-18 during the pollen period in Year 3, was analysed by ANCOVA. Asthma presence at baseline was a pre-specified covariate. Treatment by asthma status interaction was tested.

**Results:** Among 581 patients included in the Year 1 full analysis set, 14.1% were asthmatic, with 17.7% in the 4M group and 12.2% in the 2M group. Asthma status was not a significant predictor of outcome. Interaction between treatment and asthma status was not significant (p=0.62) indicating that treatment effect was independent of asthma status.

**Conclusion:** Efficacy and tolerability of 300IR 5-grass pollen sublingual tablet in patients with grass pollen allergic rhinoconjunctivitis were similar in those with and without asthma.

**P2354**

IgE sensitisation to food allergens relates to increased airway and systemic inflammation in asthmatic children – Results from the MIDAS study. Andrea van Meijdenberg1, Christien Janse1, Malin Berthold2, Magnus Borres2, Kjell Alving3, Lennart Nordvall3, 1 Department of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden; 2 Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; 3 Clinical Asthma Research, Karolinska Hospital, Stockholm, Sweden

**Background:** Food allergens are common children with asthma and linked to asthma severity. However, the relation between IgE sensitisation to food allergens and local airway inflammation or systemic inflammation in subjects with allergic asthma has been little studied.

**Methods:** Within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS), fraction of NO in exhaled air (FeNO), serum eosinophil cationic protein (sECP) and IgE against aero- or food allergen mix was measured in 151 asthmatic children aged 10-18 years. Three asthma groups were defined: non-atopic (n=31, median age 15 yrs), IgE-sensitised to only aeroallergens (n=59, median age 15 yrs) and IgE-sensitised to both aero- and food allergens (n=61, median age 14 yrs).

**Results:** FeNO levels were 8.9 ppb (7.1, 11.1) in non-atopic asthmatics, 14.2 ppb (11.7, 17.2) in aeroallergen-sensitised asthmatics and 23.4 ppb (19.4, 28.3) in asthmatics sensitised to both aero- and food allergens (p<0.01 for all comparisons). Corresponding sECP levels for the three groups were: 9.6 ng/mL (7.9, 11.8, 11.9 ng/mL (9.7, 14.5) (p=0.55 vs. non-atopic asthma), 21.9 ng/mL (18.6, 25.7) (p<0.001 vs. each of the other two groups). Asthmatic subjects sensitised to both aero- and food allergens had higher levels of FeNO and sECP than non-sensitised or aeroallergen-sensitised subjects, after adjustments for gender, age, height, lung function, total IgE.

**Conclusions:** In conclusion, sensitisation to food allergens is common among children with allergic asthma, and is related to increased local as well as systemic inflammation. The clinical implications of these findings warrant further studies.
Conclusions: Awareness of RAs and their social burden is low. There is a need for better prevention and coordination among healthcare professionals. Patients’ associations can help increase public awareness, and must be actively involved in devising and implementing RA management and education programs.

P2357
The effects of inspiratory muscle training on the interleukin-6 response to intense volitional hyperpnoea
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Vassilakopoulos et al. (Am. J. Physiol 1999; 277:R1013–R1019) demonstrated a breathing-induced interleukin-6 (IL-6) response. Whether inspiratory muscle training (IMT) can attenuate this response is unknown. Therefore, we tested the hypothesis that the IL-6 response to volitional hyperpnoea (VH) could be reduced with IMT and investigated whether this response was related to diaphragm fatigue (assessed by phrenic nerve stimulation) and/or changes in blood lactate concentration ([Lac]b).

Twelve male participants performed either 6 weeks of pressure-threshold IMT (n=6) or placebo (PLA) training (n=6). Prior to training, a maximal incremental cycling test (max) was performed. Before and after training, participants undertook two 1 h experimental trials on separate days: passive rest or VH. In VH, they voluntarily mimicked at rest the breathing and respiratory muscle recruitment pattern equal to 70–80% of the maximum minute ventilation achieved during max. IL-6 increased (P<0.01) following the pre-training VH and was (mean ± SD) 5.02±0.63 and 4.87±0.86 pg·mL⁻¹ at 2 h post for IMT and PLA groups, respectively. [Lac]b remained (P<0.01) elevated above baseline values for the duration of VH at 1.36±0.24 and 1.29±0.18 mmol L⁻¹. The IL-6 (-29%) and [Lac]b (-11%) responses were reduced (P<0.05) for the IMT, but not for the PLA group. There were no increases in IL-6 or [Lac]b over time for either group during passive rest and no evidence of diaphragm fatigue during any trial.

In conclusion, 6 weeks of IMT reduces the magnitude of the IL-6 response to VH with no evidence of diaphragm fatigue. The reduction in IL-6 may be related to the post-IMT reduction in [Lac]b.