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OAS 01
MECHANISMS AND BIOMARKERS IN ASTHMA

OA0001 | Fixed airflow obstruction in presence of asthma is associated with elevated blood eosinophils

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Background: Fixed airflow obstruction (FAO) occurs in a subtype of asthma that is associated to more symptoms, poorer response to treatment and worse prognosis. The main aim of this study was to investigate if type 2 inflammation, assessed by exhaled nitric oxide (FeNO) and blood eosinophils (B-Eos), is found to a larger extent in asthma subjects with FAO. A secondary aim was to study if type 2 inflammation is found in non-asthmatic subjects with FAO.

Method: We included 13387 participants, aged 20-80 years, from the National Health and Nutrition Examination Survey years 2007-08, 2009-10 and 2011-12 with available FeNO, B-Eos and spirometry data. FAO was defined as postbronchodilator FEV_1/FVC-ratio under lower limit of normal.

Results: Both subjects with asthma without FAO (n = 755) and subjects with asthma with FAO (n = 220) were characterized by larger prevalence of elevated FeNO (>=25 ppb) and elevated B-Eos (>=300 cells/mm3) than non-asthmatic subjects without FAO (controls) (n = 11434): 30% and 34% vs 18% for FeNO and 31%, 47% vs. 24% for B-Eos, respectively (all *P*-values < .001). Subjects with asthma with FAO had higher prevalence of elevated B-Eos (*P* = .004) and similar prevalence of elevated FeNO (*P* = .43) compared with subjects with asthma without FAO. Subjects with FAO without asthma (n = 978) had similar prevalence of elevated FeNO and B-Eos as non-asthmatics without FAO (control group): 16% vs 18% and 29% vs 24%, respectively (both *P*-values > .05). The main findings reported above were consistent when analyzing only subjects with smoking history < 10 pack-years: elevated FeNO was found in 18% of the subjects of the control group vs 34% of asthma without FAO group vs 43% of asthma with FAO group vs 21% of FAO without asthma group, while elevated B-Eos were found in 24% of subjects within the control group vs 30% of asthma without FAO group vs 44% of asthma with FAO group vs 26% in FAO without asthma group (all *P*-values for comparisons of asthma groups with controls < .05).

Conclusion: In conclusion, asthma with FAO is related to larger extent to presence of elevated blood eosinophils than asthma without FAO while this was not found for exhaled nitric oxide. This suggests an association between eosinophil inflammation and FAO in asthma that needs to be further studied in longitudinal studies. FAO in absence of asthma is not associated to signs of type 2 inflammation, suggesting other mechanisms behind the airflow limitation in non-asthmatics.

OA0002 | Nonallergic asthma, allergic asthma and nonasthmatic respiratory allergy: Definition of discriminatory biomarkers and their epigenetic modulation

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Background: In a previous study[1], we defined specific genes related with asthma and respiratory allergy diseases, by studying the gene-expression of 94 genes in a population composed by 4 groups of subjects: healthy control (HC), nonallergic asthmatic, asthmatic allergic and nonasthmatic respiratory allergic patients. The analysis of differential gene-expression between HC and patients revealed a set of statistically relevant genes mainly associated with the asthma disease's severity: *CHI3L1*, *IL-8*, *IL-10*, *MSR1*, *PHLDA1*, *PI3* and *SERPINB2*. In this project, we analyzed if these genes and their proteins could be potential asthma biomarkers to differentiate between the 4 groups and if methylation takes part in the regulation of the gene-expression.

Method: Protein quantification was determined by ELISA or Western Blot. Statistical analyses were performed by unpaired t-test, using the Graph-Pad InStat 3 program. The sensitivity and specificity of the gene and protein expression of several candidate biomarkers for differentiating the 4 groups (and the severity of asthma) was performed by receiver operating characteristic curve (ROC) analysis using the R program. DNA extracted from peripheral blood mononuclear cells of the subjects was treated with sodium bisulfite and amplified by PCR with primers designed to amplify CpG islands near the promotor region of 5 of the most significant genes. The methylation analysis was done with the Sequenom EpiTYPER approach.

Results: In the ROC curve analysis, single genes showed a good sensitivity and specificity to discriminate some of the phenotypes. However, interesting combinations of two or three protein biomarkers were found to distinguish the asthma disease, its severity, and the respiratory allergy disease between the different phenotypes and compared to the HC subjects, using reproducible techniques in easy to obtain samples. The methylation analysis showed statistically significant differences between groups in the genes analyzed.

Conclusion: Gene and protein panels formed by single and combinations of biomarkers have been defined in easy to obtain samples and by standardized techniques, that could be useful to characterize phenotypes of asthma and respiratory allergy, but specially, to differentiate the severity of the asthmatic disease. A potential regulatory mechanism of these molecular biomarkers has been defined, being methylation a possible key factor for the differential gene-expression of these asthmatic and allergic phenotypes.

[1]Baos, S., *et al*., 2017.

OA0003 | Dysregulation of sphingolipid metabolic pathways identified by untargeted metabolomics in patients with aspirin-exacerbated respiratory disease

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Background: Patients with aspirin-exacerbated respiratory disease (AERD) are known to suffer from frequent asthma exacerbation and poor prognosis. Metabolomics approaches allow biomarker discovery and identification of disease mechanism. This study was aimed to investigate the causal pathway of AERD using untargeted metabolomics approach.

Method: A total of 36 AERD and 38 aspirin-tolerant asthma (ATA) patients were enrolled. Untargeted metabolomics profile data were generated using UHPLC/Q-ToF MS system. Balanced training and test sets were used for model validation by random forest classification. The ROC curve was generated using this predictive model composed of top 10 metabolites discriminating AERD from ATA patients. Whole blood mRNA expression of SPTLC2 was analyzed.

Results: A reliable random forest model was found for discriminating AERD form ATA (AUC = 0.85, sensitivity 91.7%, specificity 66.7%). Among top 10 metabolites discriminating AERD from ATA, 4 metabolites were identified using human metabolome database and METLIN; sphingomyelin (d18:0/13:0), N-acetylvanilalanine, oleoyl ethyl amide (OetA), and hexadecyl acetyl glycerol. Among the 4 metabolites identified, 2 metabolites (sphingomyelin (d18:0/13:0), OetA) were involved in sphingolipid metabolism. In the pathway of sphingolipid metabolism, serum 3-ketosphingosin, serum sphingomyelin (d18:8/13:0), urine palmitic amide and urine OetA were identified. The levels of serum sphingomyelin (d18:0/13:0) were significantly decreased ($P < .001$) and those of urine palmitic amide and OetA were significantly increased ($P < .001$ for both) in patients with AERD. The mRNA expression of SPTLC2 involved in sphingolipid metabolism was significantly correlated with urine levels of LTE_4 in asthmatics ($P = .010$, $r = .340$) and higher in patients with AERD than those with ATA ($P = .012$). Sputum eosinophil count and FEV_1 were significantly correlated with the mRNA expression of SPTLC2 in patients with AERD ($P = .027$, $r = .587$ and $P = .008$, $r = -.552$). The levels of urine OetA were significantly correlated with % fall of FEV_1 after lysine-aspirin bronchoprovocation test in patients with AERD ($P = .001$, $r = .478$). The levels of urine OetA were significantly increased after lysine-aspirin bronchoprovocation test in patients with AERD ($P = .022$).

Conclusion: Sphingolipid metabolic pathway was identified to be related with AERD. Untargeted metabolomics approach is promising to understand relevant patho-mechanism.

OA0004 | Allergen and rhinovirus (RV) regulation of PD-L1/PD1 in allergic asthma

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Background: Asthma exacerbations in children are often caused by Rhinovirus (RV) infections in association with airway allergen challenge. To investigate the role of RV in immune responses in asthma, we analyzed the expression of the immune checkpoint programmed cell death protein 1 (PD1) and its ligand PD-L1 in blood cells of two cohorts of preschool children with and without asthma. PD1 has been implicated in silencing anti-viral immune responses and recently we reported that acute RV infection *in vitro* induces PDL1 in the PBMCs of asthmatic children. The acute phase protein C-reactive protein (CRP) rises in response to bacterial, viral, or fungal infections. To understand if RV infections are linked to immunosuppression, we analyze PD-L1 and PD1 mRNA level in total blood cells and the CRP level in the serum.

Method: The translational studies we used are part of the European study PreDicta (Post-infectious immune reprogramming and its association with persistence and chronicity of respiratory allergic diseases). Two cohorts of pre-school children (age 4-6 years) with and without asthma were analyzed. For the murine studies, we used a well-established OVA model of allergic asthma.

Results: In these cohorts of children, we analyzed the PD1 and PD-L1 mRNA expression in total blood cells considering the presence of RV in their airways at baseline as well as the CRP level in the serum at the same time point. We could show that the mRNA level of PD-L1 was upregulated in asthmatic children with an increased CRP serum level. Beside this the mRNA level of PD-L1 further correlates with the CRP serum level in healthy as well as asthmatic children with a RV infection in the upper airways. Further, the mRNA level of PD1 was downregulated in blood cells of asthmatic children with a RV infection in the upper airways as compared to control children. Finally, we looked at PD1 and PD-L1 regulation in a murine model of asthma followed by *ex vivo* infection with Rhinovirus. In this model, we found that RV significantly upregulated PD1 and PD-L1 in lung $CD3^+$ T cells of asthmatic mice.

Conclusion: The results in the children suggest that the RV preferentially activate PD-L1 in the presence of asthma. Furthermore, PD-L1 increase correlates with CRP serum level in asthmatic children. Our translation studies indicate that RV induces T cell exhaustion in the blood of asthmatic children. These studies will open new vaccination immune strategies for the therapy of RV induced asthma.

OA0005 | House dust mite priming enhances rhinovirus-induced inflammasome activation in asthma

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Background: Environmental exposures such as house dust mite (HDM) and rhinovirus (HRV16) play an important role in the asthma development and exacerbations. To date, the mechanistic link of those factors with the inflammasome activation in asthmatic bronchial epithelium is not fully understood. Activation of inflammasome leads to the production of proinflammatory cytokine IL-1ß, which supports immune responses characteristic of severe asthma.

Method: Air-liquid interphase cultures of primary human bronchial epithelial cells (HBE) from healthy controls and asthmatic patients were treated with HDM and HRV16. Mouse models of HDM-induced asthma and poly-IC-induced lung inflammation were analyzed by next-generation sequencing, real-time-PCR, Western-blotting and confocal microscopy to evaluate mechanisms of inflammasome activation. Bronchial brushings, biopsies and bronchoalveolar lavage fluid (BAL) samples from control and asthmatic subjects at baseline and/or after experimental *in vivo* HRV16 infection were analyzed using gene array, confocal microscopy and multiplex immunoassays to extend findings from *in vitro* and animal models to man.

Results: We found full activation of inflammasome in response to HRV16 represented by enhanced secretion of IL-1ß, formation of ASC specks and presence of activated caspase-1, which was further increased by HDM stimulation especially in asthmatic HBE. Release of IL-1ß was decreased by caspase-1 inhibitor and ICAM-1 blocking, but not by specific NLRP3 inflammasome inhibitor. Observed *in vitro* polarized production of IL-1ß mirrored increased IL-1ß levels in BAL fluid from asthmatic patients and *ex vivo* apical expression of ASC and RIG-I protein in epithelium in human lung biopsies. Upregulation of genes encoding RIG-I, caspase-1, IL-1ß and other inflammasome-related molecules in *in vitro* HRV16-infected HBE, mirrored by similar gene and protein expression pattern in asthmatic lung biopsies after *in vivo* rhinovirus infection suggests RIG-I as a potential sensor molecule for inflammasome activation during viral infection. Notably, there was a significant upregulation of virus- and inflammasome-related gene expression in the bronchial brushings from asthmatic patients as compared to healthy controls after *in vivo* HRV16 infection. Additionally, inflammasome signature of lungs from mouse models of HDM-induced asthma and poly-IC-induced lung inflammation has been confirmed.

Conclusion: HDM priming enhances HRV16-induced inflammasome activation in asthmatic bronchial epithelium.

OA0006 | Dietary nitrate supplementation increases fractional exhaled nitric oxide: Implications for the assessment of airway health in athletes

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Background: Fractional exhaled nitric oxide (FeNO) is a simple tool that has an established role in the assessment of airway inflammation in athletes. Specifically, FeNO provides information concerning asthma phenotypes, aetiology of respiratory symptoms, response to anti-inflammatory agents, course of disease and adherence to medication. It is recognised that FeNO can be influenced by a variety of external factors (e.g. atopic status, exercise, respiratory tract infection); however, there remains limited research concerning the impact

of dietary nitrate ingestion. The primary aim of this study was therefore to evaluate the effect of acute dietary nitrate supplementation on FeNO and resting pulmonary function parameters.

Method: The study was conducted as a randomised double-blind placebo-controlled trial. Thirty male endurance trained athletes (age: 28 ± 6 yrs; BMI: 23 ± 2 $kg.m^{-2}$) free from cardio-respiratory and metabolic disease, and stable at time of study entry (i.e. entirely asymptomatic without recent respiratory tract infection) attended the laboratory on two separate occasions. On arrival to the laboratory, athletes consumed either 140 ml nitrate-rich beetroot juice (15.2 mmol nitrate) (NIT) or nitrate-depleted beetroot juice (0 mmol nitrate) (PLA). In accordance with international guidelines, all athletes performed resting FeNO and forced spirometry (2.5 hrs post ingestion). Airway inflammation was evaluated using established FeNO thresholds: (intermediate [≥25 ppb] and high [>50 ppb]).

Results: All athletes demonstrated normal baseline lung function (FEV_1 % predicted > 80%). A three-fold rise in resting FeNO was observed following NIT (median [IQR]): 32 ppb [37] in comparison to PLA: 10 ppb [12] ($P < .001$). Twenty-two athletes (73%) presented with raised FeNO following NIT (intermediate: n = 13; high: n = 9) in comparison to four athletes (13%) following PLA (intermediate: n = 2; high: n = 2). Despite this, no difference was observed in any pulmonary function parameters between visits ($P > .05$).

Conclusion: Dietary nitrate ingestion should be considered when employing FeNO for the assessment of airway health in athletes. Our findings have implications concerning the decision to initiate or modify inhaler therapy. Further research is therefore required to determine the impact of chronic dietary nitrate ingestion on pulmonary function and bronchoprovocation testing in athletes with pre-existing asthma and/or exercise-induced bronchoconstriction.

SUNDAY, 2 JUNE 2019
OAS 02
DIAGNOSIS OF DRUG HYPERSENSITIVITY

OA0007 | Diagnostic testing for penicillin allergy: Practices and cost perceptions in Europe and North America

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Background: Having a penicillin allergy label associates with worse healthcare outcomes and increased costs. However, whether penicillin allergy testing is cost-saving remains unclear. Therefore, we aimed to assess the practice and cost perceptions of penicillin allergy diagnostic tests and procedures through a survey of drug allergy experts.

Method: We developed an online questionnaire, which was sent to European and North American drug allergy experts. Cost perceptions were assessed by inquiring about material, personnel and facilities cost estimates, and paid amounts of each test/procedure (e.g., by the State, insurance companies or patients). We analyzed reported cost estimates by respondents' region and work setting (public/private) using multiple linear regression models to identify variables associated with reported cost estimates of each test/procedure.

Results: We obtained 51 responses from 19 different countries. Intradermal and drug provocation tests (DPT) were the most commonly performed tests (median: 80% of patients labeled as penicillin-allergic). Median reported cost estimates and paid amounts were highest for desensitization ($325.9 and $174.6, respectively) and DPT ($221.2 and $133.0), and lowest for intradermal ($77.5 and $34.9) and skin prick tests ($58.2 and $33.5). North American respondents reported higher cost estimates of skin prick tests, intradermal tests and desensitizations. Higher cost estimates in multivariable models were associated with the number of involved healthcare professionals, and working in Northwestern Europe.

Conclusion: Practice and cost estimates of penicillin allergy testing are heterogeneous, requiring context-based cost assessments. The paid amounts are frequently lower than reported cost estimates which may negatively influence penicillin allergy diagnostic practices.

OA0008 | Cephalosporins allergy testing is recommended in patients with anaphylaxis to penicillins

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Background: Avoidance of cephalosporins prescription in patients with penicillin allergy has been associated with an increase of adverse events, higher incidence of bacterial resistant infections, and failure of treatment. Due to the low cross-reactivity existing between penicillins and cephalosporins, recent approaches suggest that the cephalosporins administration to penicillin allergy patients without previous skin testing can be a safe alternative in low-risk patients. We have evaluated the risk of administering a side chain unrelated cephalosporin, cefuroxime, to patients with a confirmed penicillin allergy.

Method: We included in our study 322 patients with positive result for skin tests (ST), specific IgE or a positive drug provocation test (DPT) Reagents used for STs included: Major and minor

determinants of benzylpenicillin (Benzylpenicilloyl-octa-L-lysine and bencylpenilloate, DAP-Diater, Madrid, Spain), benzylpenicillin, amoxicillin, and cefuroxime. Specific IgE to penicilloyl G, penicilloyl V, ampicilloyl and amoxicilloyl was performed (ImmunoCAP System; Phadia- AB, Uppsala, Sweden) in 183 patients. In patients with negative STs to cefuroxime, a DPT with this drug was proposed. Write informed consent was obtained from all patients for STs, specific IgE, and DPTs.

Results: The most common clinical reaction was urticaria (53.3%) followed by the anaphylaxis (34.3%). Of 332 patients, 277 (73.4%) had positive STs; 13 patients (3.9%) with negative STs had a positive specific IgE; and 42 patients (12.8%) had a positive DPT. Skin tests with cefuroxime were performed to all 332 patients. Nineteen of these had a positive ST with cefuroxime (5.7%). This positive result was associated with a previous history of anaphylaxis related to amoxicillin/amoxicillin-clavulanic ($P < .001$). A total of 153 out of 154 patients that received cefuroxime tolerated the antibiotic (99.4%). Only one patient (0.6%) had a mild urticarial reaction in the DPT with cefuroxime. Adrenaline was not required.

Conclusion: Our results confirm the low cross-reactivity (existing) between penicillins and side chain unrelated cephalosporins. Although low, the risk of developing a reaction does exist; therefore, we consider that an allergy evaluation should be performed before the administration of these drugs, especially in patients with previous history of anaphylaxis.

No potential conflict of interest was reported by the authors.

OA0009 | Short and extended provocation tests have similar negative predictive value in non-immediate hypersensitivity to beta-lactams in children

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Background: Drug provocation tests (DPTs) are the gold-standard method to diagnose non-immediate hypersensitivity reactions (NIHSR) to beta-lactam antibiotics (BL) in children. Our aim was to compare the negative predictive value (NPV) of one-day (short) DPT *versus* 3-7 days (extended) DPT for the diagnosis of NIHSR to BL in pediatric age. A secondary aim was to compare confidence on drug re-exposure after short and extended negative DPTs.

Method: The occurrence of HSR on drug re-exposure and drug refusal after negative diagnostic DPTs were evaluated in children/adolescents with a history of NIHSR to BL using a questionnaire performed 6 months to 10 years after DPT. Patients were divided into two groups according to the protocol performed: short DPT *vs* extended DPT.

Results: We enrolled 212 children and adolescents (86 females, 126 males, mean age at DPT 5.52 years, p25 = 3 years, p75 = 7.25 years): 69 tested with short DPT and 143 with extended DPT. The NPV of both types of DPT together was 95.2%. The NPV of short DPT was 97.5% and the NPV of extended DPT was 93.8% ($P = .419$). After negative DPT, beta-lactams were refused by carers in 14.75% of the children requiring subsequent treatment, 6.98% in the short DPT group and 18.99% in the extended DPT group ($P = .074$).

Conclusion: In our paediatric sample, prolonging drug administration did not increase the NPV of diagnostic DPT for NIHSR to BL or reduced drug refusal. Altogether, the data here reported suggest that, however intuitive, prolonging DPT is not beneficial in the parameters analysed.

OA0010 | Immediate hypersensitivity to iodinated contrast media: Interest of intravenous challenge test with low dose in addition of skin-testing

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Background: Frequency of immediate hypersensitivity reaction (IHR) is reported to be 0.7 to 3% in patients receiving Iodinated contrast media (ICM) and up to 0.02 to 0.04% for severe reactions. In this observational study, we compared two strategies: only skin tests assessment, and both skin tests and intravenous challenge with negative tested ICM. We evaluated the negative predictive value (NPV) of these two strategies, using as gold standard the occurrence of IHR after a full dose of ICM injection during a scheduled radiologic examination.

Method: All patients referred to the Allergy department of the Metz Regional Hospital, France, from January 2016 to December 2017, with a compatible clinical history of IHR, were included. Skin tests were performed including skin prick tests and intradermal reaction.

An intravenous challenge was performed with an ICM negatively tested. The challenge started with administration of placebo and followed by a 2 steps progression: 1 ml and 10 ml of ICM.

Results: 86 patients with full allergy assessment skin tests and intravenous challenge to ICM after a history of immediate hypersensitivity to ICM were included. An ICM exposure after the allergy check-up was found in 33 patients. Among the 86 included patients, 447 ICM were skin tested. Fifty-five (12%) skin tests were positive. Among the 33 patients with ICM re-exposure after allergy assessment, 182 ICM were skin tested. Twenty-two (12%) skin tests were positive.

86 patients were challenged with negatively skin tested ICM. Eight patients (9%) patients presented an adverse reaction during challenges.

In total 33 patients were re-exposed, corresponding to 48 ICM injections.

Out of these 48 ICM exposures, 42 (29 patients) were ICM negative to skin tests. Three hypersensitivity reactions were observed. The NPV was 92.9% (false positives rate: 7.1%).

Out of the 48 ICM exposures, 31 (23 patients) were ICM negative to skin tests and intravenous challenge. One mild hypersensitivity reaction was observed. The NPV was 96.8% (false positives rate 3.2%).

Conclusion: Our study suggests that the association of skin tests and IV challenge is more efficient than skin tests alone to identify safe alternatives for further real-life injection of ICM and seems to be cut in half the false positives rate when considering skin tests and IV challenge, in comparison to skin test only.

OA0011 | Tryptase determination as a complementary criterion for the diagnosis of perioperative anaphylaxis

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Background: The diagnosis of perioperative anaphylaxis remains challenging. Current international guidelines rely on clinical diagnostic criteria, while laboratory findings, notably tryptase determination, are viewed as an optional support. The transient increase in serum total tryptase and the detection of serum mature tryptase have been proposed as diagnostic tools. We set out to determine the contribution of tryptase determination to a more accurate diagnosis of perioperative anaphylaxis.

Method: A retrospective study was performed on 102 adult patients from the Aix-Marseille University Hospitals who had experienced a perioperative hypersensitivity reaction clinically suggesting anaphylaxis. EAACI and ICON criteria were used to diagnose anaphylaxis. Mature and total serum tryptase levels were measured.

Results: Based on EAACI guidelines, clinical diagnostic criteria for anaphylaxis were found in 76 patients and lacked in 26. For total tryptase interpretation, we applied the international consensus recommendation of 2012 that acute total tryptase levels should be greater than [(1.2xbaseline tryptase) + 2] µg/L to be considered a clinically-significant rise. In our cohort, this algorithm achieved 94% PPV, 53% NPV, 75% sensitivity, 86% specificity, and a Youden's index value of 0.61. A detectable acute mature tryptase level showed lower sensitivity, particularly in patients with acute total tryptase levels lower than 16 µg/L.

Conclusion: Serum total tryptase levels discriminated between non-anaphylactic and anaphylactic events in a perioperative setting when acute and baseline levels were collected and analyzed by the consensus algorithm. Our results suggest that acute and baseline tryptase determination may improve the diagnosis of perioperative anaphylaxis and incentivize the subsequent allergy work-up.

OA0012 | Severe cutaneous adverse drug reactions: Diagnostic approach

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Background: Severe cutaneous adverse reactions (SCAR) are rare conditions that can result in disability or death. They comprise drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), acute generalized exanthematous pustulosis (AGEP) and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN). Delayed immune hypersensitivity and genetic predisposition are involved in their pathogenesis. To describe phenotypes and suspect drugs, clinical and laboratory profiles and HLA-alleles related to SCAR identified by a systematized approach.

Method: Patients who were diagnosed with SCAR between March 2011 and August 2018 at a university hospital were included. Clinical diagnosis of phenotypes was according with the multinational registry of SCAR (Euro/RegiSCAR) and grading system criteria, while the etiology was presumed by chronological criteria, drug notoriety and application of causality algorithms. In order to collect relevant clinical and laboratory data in the acute and remission phases, the European Network for Drug Allergy (ENDA) questionnaire was used. Socio-demographic variables included age, gender and skin color/ethnicity. Drug patch tests (DPT) and HLA-ABDR genotyping (PCR-RSSO-ONELAMBDA) were carried out.

Results: A total of 65 patients were included: 33 (57.77%) with SJS/TEN, 27 (41.53%) DRESS/HSS, 3 (4.61%) AGEP and 2 (3.07%) overlap (DRESS/SJS and DRESS/AGEP). Anticonvulsants (n = 32/49.2%) were the mainly involved drug followed by antibiotics (n = 24/36.9%), analgesics/NSAID (n = 14/21.5%) and allopurinol (n = 11/16.9%). The median age was 31 years (IQR = 14-54), most were female (n = 32/49.23%) and brown/mestizos (n = 34/52.30%). Two patients with DRESS died during the acute phase. Positive DPT were shown in five carbamazepine (5/83.6%) and one phenobarbital (1/100%) associated DRESS. The HLA-ABDR typing was performed in fifty-eight (n = 58/89.2%) patients. Eight of them (n = 8/13.8%) presented HLA risk alleles, B*57 (n = 1), B*58 (n = 5) and A*31 (n = 2) were related to abacavir, allopurinol and carbamazepine SCAR respectively.

Conclusion: The diagnosis of SCAR is challenging and requires a high index of suspicion. A systematized approach helps the phenotypic and etiologic diagnosis as also the management of these patients.

SUNDAY, 2 JUNE 2019
OAS 03
ANGIOEDEMA

OA0013 | Acquired C1-inhibitor deficiency with recurrent angioedema: Spectrum and treatment with C1-inhibitor concentrate

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Background: The purpose was to describe characteristics and associated disorders of patients with acquired angioedema due to C1-inhibitor deficiency (AAE-C1-INH) and assess the efficacy of plasma-derived C1-INH concentrate (pdC1-INH).

Method: 46 patients with AAE-C1-INH were assessed for associated disorders. In 34 of the patients, the duration of swelling attacks was measured before and after treatment with pdC1-INH. The time between injection and disappearance of symptoms was recorded and treatment evaluations were provided by the patients.

Results: The following associated disorders were present: monoclonal gammopathy of undetermined significance (45.7%), non-Hodgkin lymphoma (28.3%), anti-C1-INH autoantibodies alone (10.9 %), and other conditions (6.5%). In 8.7% patients, no associated disorder could be found. AAE-C1-INH led to the detection of lymphoma in 76.9% of patients with the malignancy. Treatment with pdC1-INH shortened attacks by an average 54.4 (±32.8) hours ($P < .0001$). The earlier the attack was treated, the shorter the time between injection and disappearance of symptoms (P = .0149). A total of 3557 (97.7%) of 3640 treated attacks were effectively treated with pdC1-INH as assessed by the patients. pdC1-INH was effective in 1246 (93.8%) of 1329 attacks in 8 patients with anti-C1-INH autoantibodies and in 344 (99.4%) of 346 attacks in 6 patients without autoantibodies. The average dose per effectively treated attack was 1238.4 U in patients with anti-C1-INH autoantibodies and 510.2 U in patients without autoantibodies.

Conclusion: pdC1-INH is highly effective in treating AAE-C1-INH patients. It reduces attack duration and is fast-acting. It is also effective in the vast majority of attacks in patients with anti-C1-INH autoantibodies.

OA0014 | Effects of long-term prophylaxis with subcutaneous C1 inhibitor in special patient populations: Findings from the COMPACT open-label extension trial

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Background: Subcutaneous C1 inhibitor (C1-INH [SC]) replacement therapy is indicated for routine prophylaxis of hereditary angioedema (HAE) attacks in adolescents and adults. This *post-hoc* analysis of the open-label extension (OLE) of the Phase III COMPACT study examined the safety and efficacy of C1-INH (SC) in special populations: paediatric patients (≤17 years old), geriatric patients (≥65 years old) and female patients who became pregnant on study treatment.

Method: In the COMPACT OLE study, 126 eligible patients with type I/II HAE (≥6 years old, experiencing ≥ 4 attacks/2-month interval) were randomly assigned to receive C1-INH (SC) at 40 IU/kg or 60 IU/kg twice weekly for 52–140 weeks. In this *post-hoc* analysis, patients were stratified by age (≥65 and < 65 years, and ≤ 17 and > 17 years for the geriatric and paediatric analyses, respectively). Percentage of responders (i.e. those experiencing ≥ 50% reduction in attacks relative to baseline), HAE attack rate, safety endpoints and patient profiles were evaluated for each subgroup. Patients who conceived during the trial were withdrawn from treatment when pregnancy was identified and were followed up to assess pregnancy outcomes.

Results: Of the 126 patients, 10 were aged ≥ 65 years, 10 were ≤ 17 years and four patients became pregnant. Overall, 6/10 geriatric patients, 10/10 paediatric patients and 4/4 patients who became pregnant during the study had an attack rate of < 1 attack/4-weeks, of which three, one and one were completely attack-free, respectively. In total, 6/9 evaluable geriatric patients, 10/10 paediatric patients and 4/4 conceiving patients were classified as responders. No serious adverse events (AEs) were reported in the paediatric population. In two geriatric patients, serious AEs unrelated to treatment were reported, namely dehydration, hypokalaemia and pneumonia; these serious AEs resolved and did not lead to treatment discontinuation. All pregnant patients had normal pregnancy outcomes and delivered healthy infants.

Conclusion: In the COMPACT OLE study, C1-INH (SC) was well tolerated and reduced the HAE attack rate in special patient populations.

OA0015 | Final results from the ZENITH-1 study: Oral administration of plasma kallikrein inhibitor BCX7353 for the treatment of attacks in patients with hereditary angioedema

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Grivcheva-Panovska V[9]; Hagin D[10]; Steiner U[11]; Kiani-Alikhan S[12]; Agmon-Levin N[13]; Bygum A[14]; Aberer W[15]; Faust S. N[16]; Launay D[17]; Gompels M[18]; Triggiani M[19]; Bethune C[20]; Reshef A[21]; Cornpropst M[22]; Dobo S[22]; Van Dyke S[22]; Murray S[22]; Collis P[22]; Sheridan WP[22]; Farkas H[23]; Cicardi M[3]

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Background: ZENITH-1 is a Phase 2, randomized, double-blind, dose-ranging trial evaluating the efficacy and safety of the oral plasma kallikrein inhibitor BCX7353 vs placebo as an on-demand treatment of hereditary angioedema (HAE) attacks. Analyses of the first dose (750 mg; n = 36) are available; cohorts evaluating lower doses (500 mg or 250 mg; n = 12/cohort) have completed dosing.

Method: Adults with HAE Type I or II self-administered blinded study drug to treat 3 attacks, each within one hour of symptom onset. Two attacks were treated with the same dose of BCX7353 (750 mg, 500 mg or 250 mg) and 1 with placebo in a randomized sequence. Where possible, subjects were asked to refrain from taking approved attack medication for at least 4 h post-study drug. Subjects recorded HAE symptom severity using a 3-symptom visual analog scale (VAS) and qualitative assessments prior to and at 1, 2, 3, 4, 8 and 24 h after study drug dosing. Outcomes were compared using generalized logistic regression models.

Results: Across the study, 58 subjects treated a total of 163 attacks; 30, 11 and 10 subjects treated all 3 attacks in the 750, 500 and 250 mg dose groups, respectively. There were no study-drug related Grade 3/4 AEs, lab abnormalities, or SAEs; the incidence of AEs after BCX7353- and placebo-treated attacks were similar. In the 750 mg group, the baseline composite VAS scores were 14 mm and 15 mm for BCX7353- and placebo-treated attacks, respectively; for the first postdose timepoint (1 h), there was a statistically significant reduction in composite VAS for BCX7353 compared with placebo (3 mm difference between treatments, $P = .0203$), which increased at 4 h postdose (7 mm difference, $P = .0024$). At 4 h postdose, subjects reported a stable or improved composite VAS in 68% of BCX7353-treated angioedema attacks vs 47% for placebo (OR = 2.771, $P = .0387$). At 24 h, subjects reported no or mild symptoms by patient global assessment in 64% of BCX7353-treated attacks vs 32% for placebo (OR = 4.614, $P = .0038$). Rescue medication was used in 27% of BCX7353-treated attacks compared with 60% of placebo-treated attacks (OR = 0.196, $P = .0029$). Results for all doses will be reported.

Conclusion: In this novel, early-intervention trial with subjects responsible for evaluating evolving HAE attack symptoms, BCX7353 was superior to placebo in producing rapid and sustained efficacy and was well-tolerated. These results support further development of BCX7353 as an oral on-demand treatment for HAE attacks.

OA0016 | GRK2 regulates the endothelial responsiveness to bradykinin: Role in C1-inhibitor- deficiency hereditary angioedema

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Background: Bradykinin (BK) regulates vascular homeostasis through the endothelial Gq protein-coupled receptors (B1-B2), using Ca2 + as second messenger. Several kinases are involved in the regulation of BK signaling, such as CamKII; also GRK2 could be involved as it is able to phosphorylate BK receptors but with unknown biological effects. Our aim is to verify the role of GRK2 in regulation of BK signaling in physiological and pathological conditions.

Method: *In vitro*, Bovine Aortic Endothelial cells (BAEC) was used to determine GRK2 modulation by western blot, Ca^{2+} release and Nitric Oxide (NO) production by Fluo4 and DAF-FM probes. In mice with endothelial GRK2 Knock out (endGRK2 KO) we performed a Miles assay to test vascular permeability. In PBMCs from patients with C1- inhibitor- deficiency hereditary Angioedema (C1- INH- HAE) we evaluated GRK2 levels by western blot

Results: At 5 min, BAEC stimulation with BK (100 nM) induced an increase of GRK2 in all cellular compartments returning to baseline levels at 15 min. This accumulation is proteasome dependent, since GRK2 ubiquitination was significantly reduced post BK stimulation. We hypothesized that CamKII activated upon BK stimulation regulates GRK2 accumulation. Indeed, GRK2 and CamKII interaction increased post BK and the accumulation of GRK2 does not occur after CamKII inhibition, supporting our hypothesis. Ca^{2+}cytosolic accumulation induced by BK was enhanced by inhibition of GRK2 with KRXC7. Accordingly, permeabilization and NO induced vasodilation, typically endothelial responses to BK, were also enhanced with GRK2 inhibition. To test *in vivo* the regulation of BK-dependent endothelial responses by GRK2 we evaluated BK-induced vascular permeability in endGRK2-KO mice. Interestingly, these mice showed an increased vascular permeability already in basal condition and an increased response to BK respect to wt mice. Since GRK2 regulates the sensitivity of endothelium to BK, we speculated that GRK2 could have a role in BK- mediated Human Angioedema. We evaluated GRK2 levels in C1- INH- HAE patients

evidencing that patients with reduced GRK2 levels showed a more severe phenotype.

Conclusion: Through CamKII, BK activates GRK2 which in turn acts as endogenous inhibitor of BK signalling, in vitro and in vivo. Consistently, patients with severe Angioedema have reduced levels of GRK2, suggesting that GRK2 contributes to BK-dependent pathological response of endothelium during Angioedema

OA0017 | Effects of subcutaneous C1-esterase inhibitor on coagulation and fibrinolysis in patients with hereditary angioedema: Findings from the COMPACT And OLE study

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Background: Activation of the contact system is observed along with increase of Prothrombin Fragment (PF) 1 + 2 (a marker of thrombin generation) and D-dimer (a marker of fibrin degradation) during attacks of hereditary angioedema (HAE). Despite these, increased pro-thrombotic complications are not reported in HAE patients. We evaluated the effects of prophylactic subcutaneous C1-esterase inhibitor (C1-INH [SC]) on pro-coagulant markers in HAE patients treated in the COMPACT (N Engl J Med 2017; 376:1131-1140) and OLE studies.

Method: In the COMPACT study, subjects received 40 IU/kg or 60 IU/kg of plasma-derived C1-INH (SC) and a corresponding placebo, as prophylaxis over 16 weeks each. In a subsequent open-label extension (OLE), subjects received 40 IU/kg or 60 IU/kg of C1-INH (SC) for up to 140 weeks. We evaluated the effects of 60 IU/kg C1-INH (SC) on coagulation and fibrinolytic parameters (D-dimer, PF 1 + 2, activated Partial Thromboplastin Time [aPTT], Fibrinogen, Prothrombin International Normalized Ratio [PT-INR], and PAP [Plasmin-α2-antiplasmin] complex).

Results: In both COMPACT and OLE studies median levels of coagulation and fibrinolytic parameters (D-dimer and PF 1 + 2) were mildly raised at baseline and normalized at Week 14 (COMPACT) and at End-of Study Week 53/88 (OLE), as follows: D-dimer COMPACT: 605.0 to 330.0 ng/mL; OLE: 510.0 to 360.0 ng/mL and PF 1 + 2 COMPACT: 264.0 to 185.0 pmol/L; OLE: 218.5 to 193.5 pmol/L. The aPTT, Fibrinogen, and PT-INR levels were stable relative to baseline over the whole treatment periods. A normalization of PAP complexes was also seen with 60 IU/kg C1-INH (SC). Results are only presented for the Food and Drug Administration (FDA) approved 60 IU/kg dose.

Conclusion: A pharmacodynamic effect of prophylactically administered C1-INH (SC) on pro-coagulant markers indicates that hemostatic balance was restored with continuous C1-INH replacement therapy. Further research is warranted to explore the potential of coagulation-fibrinolytic parameters as a biomarker of disease activity in HAE.

OA0018 | Angiotensin-converting enzyme inhibitor-associated angioedema in a cohort of Italian patients: From bed to bench

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Background: Angiotensin-converting enzyme inhibitor-related angioedema (ACEI-AAE) occurs in 0.1-0.7% of patients (pts) treated with ACEI. Diagnosis is based on exclusion of other causes of angioedema (AE) in pts with recurrent AE taking ACEI. We have recently discovered that pts with hereditary AE with C1 inhibitor deficiency (C1-INH-HAE) have increased plasma levels of vascular endothelial growth factors (VEGFs), angiopoietins (Angs) and secreted phospholipases A_2 (sPLA$_2$s), which are involved in vascular permeability. We present the clinical features and plasma levels of VEGFs, Angs and activities of sPLA$_2$s in a cohort of pts with ACEI-AAE followed up at the AE Centers of Universities of Naples and of Zagreb.

Method: Pts with history of AE without wheals after the start of ACEI therapy were studied. C1-INH deficiency and allergological causes were ruled out. Pts' demographic information, clinical features of AE and comorbidities were obtained from each pt's chart and interview. Concentrations of VEGF-A, VEGF-C, Ang1 e Ang2 were evaluated by ELISA in pts with ACEI-AAE in symptoms free period and controls. In the same population, sPLA$_2$s enzymatic activity was evaluated using magnetic stirrer Fluorescence.

Results: 51 Caucasian pts (43%F) were diagnosed with ACEI-AAE. The average time of symptoms onset after starting ACEI was 3 years (yrs) (range (r),0.4-20 yrs); 4 yrs was the average of therapy duration. The estimated diagnostic delay was 1 yr. Lips were the most common affected site (74.5%); 52% of pts described tongue involvement. In 15 cases there was larynx edema (29.5%). 63% of pts required hospitalization, with no endotracheal intubation. 9 pts complained itching and 3 presented skin rash during attacks. After the end of ACEI therapy, 36% of pts who started sartans (9pts) and 29% of pts who switched to other anti-hypertensive drugs (7 pts) had AE. Pts with ACEI-AAE in symptom-free period have elevated levels of

VEGFs and $sPLA_2$ compared to controls. Ang concentrations are not modified.

Conclusion: ACEI-AAE is a rare side effect but it can be a medical emergency enough to require hospitalization in the majority of pts. Discontinuation of ACEI is necessary but sometimes is not sufficient to break up AE. There is no increased risk of AE in pts who switched to sartans. Itching and rash may be present during ACEI-AEE attacks. In addition, increased plasma levels of VEGF-A, VEGF-C and $sPLA_2$ in ACEI-AAE pts may prompt the investigation of these mediators as biomarkers of ACEI-AAE.

SUNDAY, 2 JUNE 2019

OAS 04

OUTCOME MEASURES IN ALLERGEN AND IMMUNOTHERAPY

OA0019 | Efficacy and safety of the 300 IR sublingual tablet for the treatment of house dust mite-associated allergic rhinitis: A multicentre, international, dbpc, randomized phase III clinical trial

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Background: The 300 index of reactivity (IR) house dust-mite (HDM) sublingual tablet (STG320; Stallergenes Greer) for allergen immunotherapy (AIT), containing a 1:1 mixture of standardized extracts of both *Dermatophagoides pteronyssinus (Dpte)* and *Dermatophagoides farinae (Dfar)*, has demonstrated beneficial effects on allergic rhinitis (AR) in European and Japanese populations. In this large multicentre, international, double-blind, placebo-controlled, randomized Phase III clinical trial, we evaluated the efficacy and safety of a 12-month course of the 300IR HDM tablet in adults and adolescents with HDM-associated AR.

Method: Patients were screened for inclusion by 231 investigating centres in 13 countries particularly in Europe and North America. The key inclusion criteria were age 12-65, confirmed HDM allergy for at least 1 year, sensitization to *Dpte and/or Dfar* (positive skin prick tests and HDM-specific serum IgE ≥ 3.5 kU/L), and a baseline average Total Combined Score (aTCS) ≥ 5 (scale: 0-15). The TCS is the sum of the Rhinitis Total Symptom Score (RTSS) and the Rescue Medication Score (RMS), respectively scaled 0-12 and 0-3. Patients with confounding allergies or medications, recent AIT, and not controlled asthma were excluded. Eligible patients were randomized to daily treatment with the 300IR HDM tablet or a placebo tablet. The primary efficacy endpoint was the aTCS at the end of the treatment period (ANCOVA). Secondary endpoints (such as RTSS, RMS and safety) were also assessed.

Results: 1607 patients were randomized (300IR: n = 802; placebo: n = 805). The treatment groups did not differ notably with regard to gender ratio, age, HDM AR duration, asthma, baseline aTCS or treatment compliance. In the primary analysis, there was a significant statistical difference between treatment groups ($P < .0001$). The relative least squares mean difference ([95% confidence interval]) versus placebo was −16.9% [−24.0%; −9.2%]. Improvements vs placebo in the secondary endpoints RTSS and RMS were also significantly reduced in the 300IR group vs placebo. The AIT tablet was generally well tolerated. No unexpected serious adverse reactions were observed. The most commonly reported adverse events were application site reactions of mild or moderate severity (i.e. oral pruritus, throat irritation).

Conclusion: This large trial confirmed the efficacy and favourable safety profile of the 300IR HDM tablet for AIT in adults and adolescents with HDM-associated AR.

OA0020 | The SQ Tree SLIT-tablet provides significant improvement of nasal and ocular symptoms during the tree pollen season

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Background: In Europe and North America, seasonal allergy is often caused by tree pollen from members of the birch homologous group (e.g. birch, alder, and hazel). Most tree pollen allergic patients report rhinitis and conjunctivitis symptoms during the pollen season.

The SQ tree SLIT-tablet has been developed for treatment of allergic rhinoconjunctivitis induced by pollen from the birch homologous group. Clinical efficacy was investigated in a phase III, randomised, DBPC trial (EudraCT 2015-004821-15). Here we report the treatment effect on nasal symptoms and ocular symptoms.

Method: 634 subjects (12-65 years) with moderate-severe allergic rhinoconjunctivitis despite symptomatic treatment were randomised

1:1 to SQ tree SLIT-tablet (12 SQ-Bet) or placebo for ≥ 16 weeks prior to and throughout the tree pollen season (TPS; defined as the alder, hazel, and birch pollen seasons, i.e. not necessarily one continuous period). During the TPS, subjects rated 4 rhinitis and 2 conjunctivitis symptoms on a daily basis. Primary efficacy was assessed as the total combined score (TCS) during the birch pollen season (BPS), i.e. the sum of the average daily symptom score (DSS) and the average daily medication score.

Results: The primary analysis showed a 40% lower TCS during the BPS for subjects treated with 12 SQ-Bet compared to subjects on placebo (absolute score difference 3.02, $P < .0001$ (Biedermann et al. 2019)).

Post-hoc analyses of rhinitis symptoms and conjunctivitis symptoms during the BPS showed that treatment with 12 SQ-Bet resulted in a 35% reduction in rhinitis DSS (absolute score difference 0.88) and a 45% reduction in conjunctivitis DSS (absolute score difference 0.43) compared to placebo ($P < .0001$ for both). Similar results were observed when analysing rhinitis and conjunctivitis symptoms during the TPS: treatment with 12 SQ-Bet resulted in a 31% reduction in rhinitis DSS (absolute score difference 0.65) and a 40% reduction in conjunctivitis DSS (absolute score difference 0.33) compared to placebo ($P < .0001$ for both).

Conclusion: Treatment with the SQ tree SLIT-tablet significantly improved rhinitis symptoms and conjunctivitis symptoms not only during the BPS but also during the TPS. These post-hoc findings highlight that the overall treatment benefit involves clinical improvement of both nasal and ocular symptoms experienced by patients with allergic rhinoconjunctivitis induced by pollen from the birch homologous group.

OA0021 | Treatment failure in bee venom immunotherapy: Too early to reach any conclusion regarding Api M 10

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Background: Venom immunotherapy (VIT) provides long-term protection from further systemic sting reactions in as many as 95-99% of patients treated with vespid venom, and 75-85% of patients treated with bee venom. It has been consistently shown that bee VIT is less effective than vespid VIT, but underlying reasons are still unclear. Predominant Api m 10 sensitization was assumed to be a risk factor for treatment failure because Api m 10 could be absent or underrepresented in some therapeutic venom preparations.

Method: In an ongoing study evaluating the efficacy and safety of an accelerated up-dosing protocol, we included 76 patients with vespid VIT and 25 with bee VIT. Bee VIT was performed with a purified aluminum hydroxide adsorbed bee venom preparation where a loss of Api m 10 immunoreactivity has been postulated. We determined specific IgE levels to bee and vespid venom as well as to all available venom allergens before VIT and immediately before sting challenges. Sting challenges were performed, whenever possible, one week after reaching the maintenance dose. Sensitization was considered predominant if the proportion of sIgE to a single venom allergen was at least 65% of the sIgE to the venom preparations.

Results: While 100% of patients treated with vespid VIT tolerated sting challenges, the effectiveness was 88% (22/25) in patients treated with bee VIT. Predominant sensitization to one bee venom component was detected in 10 patients who tolerated sting challenges and in all three patients who relapsed: 14% (3/22) of the responders showed a predominant sensitization to Api m 1, 9% (2/22) to Api m 2 or Api m 3 respectively, and 14% (3/22) to Api m 10. Two of the three non-responders were predominantly sensitized to Api m 2 and the third patient showed a predominant Api m 5 sensitization.

Conclusion: These preliminary data show that also other predominant sensitizations may be relevant as risk factors for treatment failure. Interestingly, all patients with a predominant Api m 10 sensitization who received bee VIT with a venom preparation with a supposed lack of Api m 10 tolerated sting challenges. Therefore, a multicenter study with a sufficient number of patients with treatment failure is urgently required before any conclusion can be reached.

OA0022 | The cambridge peanut allergy clinic: Real world safety and efficacy outcomes during oral immunotherapy with characterised peanut flour

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Background: To report patient outcomes of tolerability, safety and real-world efficacy of a peanut oral immunotherapy regimen.

Method: At the Cambridge Peanut Allergy Clinic (Camallergy, UK), a standardised daily regimen with encapsulated, characterised peanut flour manufactured to good manufacturing practices (GMP) involves seven short up-dosing clinic visits (two weeks apart over four months) followed by daily maintenance (200 mg protein). Characterised peanut flour is emptied from the pull-apart capsules into food, which is then consumed. The initial up-dosing requires a brief appointment where a single low dose (2 mg) is administered and, if tolerated, taken daily at home for two weeks. Doses are then increased every two weeks, under supervision, as tolerated. Severely allergic patients were included: 16% had used adrenaline (some used two doses) for historical reactions and 56% had asthma. Daily symptom diaries were collected at each clinic visit. In this evaluation, side-effect and tolerability data were recorded for 110 patients aged 7-17y.

Results: 32,900 doses were administered (10,569 up-doses and 22,331 maintenance doses over 4-24 m); 84% of up-dosing and 97% maintenance days were symptom-free. The initial up-dosing

was well tolerated with at most only minor symptoms and no withdrawals. Of symptoms on up-dosing, 75% were mild/transient with oral pruritus (32%) or abdominal ache (43%), requiring no treatment or, in 12%, only oral antihistamine. Respiratory symptoms (mostly mild) occurred after 4% of up-doses and 0.2% of maintenance doses. Oral antihistamines were used during up-dosing in 50% of patients (2% of doses) and asthma inhalers in 11% of patients (0.32% doses). Adrenaline was used in two patients during up-dosing and two in maintenance (0.015% of doses). Of these, three continued to tolerate the maintenance dose and one was withdrawn because of a generalised allergic reaction. Three others withdrew for non-treatment-related reasons (overall withdrawal = 3.6%).

Conclusion: A seven-stage regimen achieving maintenance dosing in 3.7 months using characterised peanut protein and was well tolerated, with few reactions and mostly minor symptoms; 96% of patients successfully were able to continue to take the maintenance doses. The single, low-dose initial up-dosing was very well tolerated and safe. Adrenaline was rarely used, and the withdrawal rate was far lower than that reported in published trials.

OA0023 | ARTEMIS: A European, phase 3, randomised, double-blind, placebo-controlled trial of AR101 in peanut-allergic children and adolescents aged 4-17

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Background: The investigational oral biologic drug AR101 is a potential immunomodulatory treatment for peanut allergy. ARTEMIS is a pivotal phase 3, randomised, double-blind, placebo-controlled trial investigating the efficacy and safety of AR101 oral immunotherapy (OIT) in European peanut-allergic subjects. A preliminary review of baseline characteristics is presented here.

Method: Eligible subjects aged 4-17 years were enrolled in 7 European countries: France, Germany, Ireland, Italy, Spain, Sweden and UK. Key entry criteria included sensitisation to peanut on skin prick test (SPT) and/or peanut-specific IgE (psIgE) and dose-limiting symptoms to ≤ 300 mg peanut protein at baseline double-blind, placebo-controlled food challenge (DBPCFC). Subjects with a clinical history of severe anaphylaxis to peanut could be eligible. Subjects were randomised 3:1 to AR101 or placebo, up-dosed on day 1 and received dose escalations every 2 weeks for 20-40 weeks followed by approximately 3 months of 300 mg/day maintenance. The primary endpoint was the ability to tolerate at least 1000 mg peanut protein as a single dose without dose-limiting symptoms at exit DBPCFC

Results: 175 peanut-allergic children aged 4-17 years were randomised. At the time of abstract submission, 169 of 175 subjects have completed the exit DBPCFC. The median age at baseline was 9 years (range 4-17) and 95 (54%) subjects were male. 75 (43%) subjects had a history of controlled mild-to-moderate asthma, 102 (58%) had atopic dermatitis, 84 (48%) had allergic rhinitis and 100 (57%) had multiple food allergies. At baseline, the median (Q1-Q3) peanut SPT was 11 mm (9-15), median (Q1-Q3) psIgE was 51.8 kU_A/L (6.5-132.0) and the median (Q1-Q3) tolerated dose of peanut protein at screening DBPCFC was 10 mg (3-30).

Conclusion: ARTEMIS is a pivotal phase 3 study investigating the safety and efficacy of AR101 after 3 months of maintenance therapy in Europe. Baseline results indicate a highly allergic population with a high prevalence of comorbidities who react to low doses of peanut protein at screening DBPCFC. ARTEMIS, which will complete in early 2019, will advance the field by providing critically needed data to determine the safety and efficacy of AR101 and add to our understanding of peanut-allergic patients.

OA0024 | The SQ Tree SLIT-tablet improves quality of life for subjects with moderate-severe allergic rhinoconjunctivitis

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Background: The SQ tree SLIT-tablet (12 SQ-Bet) has been shown to improve allergic rhinoconjunctivitis (ARC) symptoms and reduce the need for symptomatic treatment for subjects with ARC induced by pollen from the birch homologous group in a phase III, randomised, DBPC trial (EudraCT 2015-004821-15). Here, we present the impact of treatment on quality of life during the birch and tree pollen (alder, hazel, birch) season (BPS/TPS).

Method: 634 subjects (12-65 years) with moderate-severe ARC despite symptomatic treatment were randomised to 12 SQ-Bet or placebo for at least 16 weeks prior to and throughout the TPS.

Pollen seasons spanned 6 (BPS) and 10 (TPS) weeks. As a secondary endpoint ARC quality of life was measured by RQLQ(S) for adults and RQLQ(S) + 12 for adolescents on a weekly basis. The questionnaires are similar, except that sleep problems are not included for adolescents. Both are scored from 0 (not troubled) to 6 (extremely troubled). The weekly RQLQ scores were calculated as the average of all item scores available for each domain/all domains. The weekly RQLQ scores were analysed by a repeated measurement analysis including a treatment group-time point interaction term and pollen station as fixed factors and subject nested within pollen station as a random effect. The analysis included subjects in FAS with diary data during the season.

Results: The overall RQLQ score was significantly improved for 12 SQ-Bet compared to placebo during the BPS (absolute difference: 0.45, $P < .0001$) and the TPS (0.37, $P < .0001$). Likewise, all individual domain scores were significantly different from placebo (absolute differences: 0.38-0.51, $P < .0001$, BPS and 0.29-0.45, $P < .0001$, TPS, for all domains). The largest differences were found for: "activities" (e.g. social and outdoor activities), "eye symptoms" and "practical problems" (e.g. inconvenience of having to carry tissues or need to blow nose repeatedly). For the weekly scores, all domain scores were significantly different from placebo during weeks 2-9 of the TPS (post hoc analysis).

Conclusion: Treatment with the SQ tree SLIT-tablet improved quality of life compared to placebo during the BPS and TPS. Improvements were seen for all domain scores, with the largest differences between 12 SQ-Bet and placebo for the domains "activities," "eyes" and "practical problems." These findings substantiate the clinical relevance of the SQ tree SLIT-tablet for patients with ARC induced by pollen from the birch homologous group.

SUNDAY, 2 JUNE 2019

OAS 05

MECHANISMS AND MANAGEMENT OF SEVERE OCULAR ALLERGY, WHAT'S NEW?

OA0025 | Conjunctival transcriptome analysis reveals the overexpression of multiple microbes-associated molecular patterns (MAMPs) receptors in vernal keratoconjunctivitis

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Background: Vernal keratoconjunctivitis (VKC) is a recurrent bilateral chronic ocular allergic inflammatory disease mostly non-IgE-mediated. The aim is to identify differences in gene expression between VKC and normal subjects (CT) and to investigate innate immunity pathways that may be involved.

Method: Conjunctival cells were collected by impression cytology (Eyeprim) from 25 VKC patients and 5 CT. Based on prior optimization of all assay steps, RNA was isolated from the samples using a Qiagen RNeasy Plus Mini Kit. The RNA integrity number (RIN) was assessed with an Agilent Bioanalyzer. Samples were then assayed with the NanoString human immunology codeset to assess the expression levels of 579 immunology-related genes.

Results: 143 genes were significantly differently expressed (DEG) in VKC vs CT samples.

The most overexpressed genes in the VKC group included several chemokines, cytokines and their receptors, several members of the leukocyte immunoglobulin-like receptors (LILR) and of the TNF receptor family. The inflammasome marker NLRP3 and several members of the microbes-associated molecular patterns (MAMPs) receptors, such as Toll like receptors (TLR)4 and TLR8, C-type lectin domain family (CLEC)4A, CLEC4E, CLEC5A, CLEC7A, mannose receptor (MRC1/CLEC13D and DC-SIGN/CD209), nucleotide-binding oligomerization domain-containing protein (NOD)2, macrophage receptor with collagenous structure (MARCO) and several of their pathway-related genes (FCERG1, CARD9, IRAK2, IRAK3, CD14, NF-kB) were significantly overexpressed.

Interestingly, one of the most over expressed genes is PTGS2, encoding for the COX-2 enzyme. The number of overexpressed genes increased with the disease severity assessed by activities clinical scores.

Conclusion: The increased expression of several chemotactic factors and co-stimulatory signals required for T cell activation and survival, confirms that VKC is mostly a cell-mediated pathology. The multiple expressions of innate-immune recognition receptors suggest a possible interaction with multiple environmental particles as an initiating factor in disease pathogenesis.

OA0026 | Autophagy in vernal keratoconjunctivitis and the role of TNF-alpha

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Background: Vernal keratoconjunctivitis (VKC) is a severe ocular allergy with pathogenic mechanism poorly understood and no efficacious treatment. The aims of the present study were to investigate the expression of autophagic markers in VKC and to explored the role of TNFα in the induction of autophagy using an *in vitro* model.

Method: Seven active VKC patients and 7 healthy, age-matched subject were included. Conjuntival biopsies were obtained and analyzed by immunohistochemistry (IHC) with specific antibodies against MAPLC3A, MAPLC3B, Beclin-1, LAMP1, Cathepsin B and D, BCL-2, BAX and Caspase 3. The positive IHC reaction was evaluated in the epithelium and subepithelial stroma of conjunctival tissues and classified as very intense (3+), intense (2+), slight (1+), very slight (+/-) or absent (0). Primary conjunctival cell cultures were treated with IL-1α, IL-4, or TNF-α and analysed by qPCR and western blotting for expression of autophagic and lysosomial markers at 4, 10 and 24 hours after exposure.

Results: IHC analysis showed that LC3B, cathepsin D, Beclin-1 and LAMP1 are over-expressed in VKC biopsies, compared to the control samples, especially by cells in the stroma. The proteins involved in apoptosis, BAX, BCL2 and Caspase 3 were less reactive in both control and VKC tissues.

In conjunctival fibroblasts, but not in epithelial cells cultures, LC3B, Beclin-1, LAMP1 and p62 strongly increased from 4 to 24 hours, whereas the expression of Cathepsin D, a protein implicated in lysosomial apoptotic pathway, was comparable to that of untreated controls. Western blotting analysis revealed cleavage and lipidation of LC3B quantified as an increased LC3BII/LC3BI ratio. Double immunofluorescence for Cathepsin D and LAMP1 showed that Cathepsin D was localized within the lysosomes at 4, 10, 24 hours after TNFα exposure to inflammatory stimuli.

Conclusion: Our data demonstrated that autophagy is present in VKC. TNFα significantly stimulates autophagy in VKC: the increase of the autophagosome adaptor LC3B and of the cargo adaptor p62 in the cells exposed to inflammatory stimuli shows the build-up of autophagosomes and the increased LC3BII/LC3BI reveals their degradation.

OA0027 | Long term efficacy of omalizumab in severe ocular allergy in children

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Background: Severe ocular allergy in children, such as Vernal keratoconjunctivitis (VKC), usually requires the use of topical steroids and cyclosporine. In most recalcitrant cases, omalizumab has been shown to be an interesting treatment, with a quick onset of action. However, little is known about the long term effect of this treatment. We report our experience of omalizumab in VKC children over the long term.

Method: We retrospectively reviewed the files of 5 boys with severe VKC treated with omalizumab for more than 12 months. Response to treatment was graded as complete (no more inflammatory flare on treatment), partial (some inflammatory flares) or absent, for VKC, asthma, rhinitis and eczema. Adverse effects were also noted.

Results: Five boys, aged 6 to 13 years old, were included. All children also suffered from asthma and rhinitis, and 4 from eczema. Polysensitization was present in all cases, as well as high serum IgE levels. Corneoconjunctival inflammation was severe, perennial and resistant to a combination of topical steroids and cyclosporine. Vernal ulcers or plaque had occurred in 2 patients, and intrapalpebral depot-steroid injections had been required in 2 children. Omalizumab was administered every 2 weeks by subcutaneous injections, at doses varying from 450 to 600 mg per injection.

Initial ocular response was graded as complete in 1 patient, partial in 3 and absent in 1, within 4 months. Partial responders had still inflammatory recurrences, but less frequent, shorter and easily controlled by short pulses of topical steroids. They also responded better to topical cyclosporine. Response for asthma and eczema was complete in all cases within 4 months, and partial in all cases for rhinitis. Median follow-up on omalizumab treatment was 37 months, ranging for 16 to 80 months. The response to treatment did not change during the follow-up. No systemic or local adverse effect occurred were noted. Omalizumab was stopped in one case after 16 months, without ocular recurrence.

Conclusion: Omalizumab is an potent treatment of severe ocular allergy in children. Response to the treatment was partial in most of our cases, but allowed for a reduced exposition to topical steroids and immunomodulators. No change of response to omalizumab was observed over the long term. No safety issues were noted.

OA0028 | Quality of life of patients affected by vernal keratoconjunctivitis: Effect of omalizumab

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Case report:

Background: Vernal keratoconjunctivitis (VKC) is a severe condition, which can result in loss of vision. We report results of a retrospective study of ocular quality life of 10 children referred to our specialized consultation in ocular allergy for management. Omalizumab (OMZ) was prescribed to enhance to reduce the alteration of quality of life (QoL).

Method: 10 patients were included in this study on quality of life (9 Males/ 1 female, aged 7-19 years). VKC symptoms were evolving for an average of 5.85 years (0.33 to 12 ys). All patients were affected with asthma, 9 were sensitized to airway allergens and 4 to food allergens. All had experienced at least one corneal ulcer during the last year before inclusion, despite ongoing treatment with topical cyclosporine. Decision was made to treat these patients affected by disabling asthma with OMZ because of the failure of the previous treatments to restrain symptoms, to avoid corneal complications and their possible iatrogenic effects. OMZ was prescribed according to the manufacturer recommendations. Ocular QoL was evaluated by the patient through a daily scoring from 0 (best QoL) to 10 (worst QoL).

Results: The mean follow-up after the first injection of OMZ was 62.90 ± 33.85 weeks ([16; 108 weeks). None of the patients experienced corneal ulcer during this period. 6 out of 10 patients disrupted cyclosporine treatment during the follow-up months. We observed benign one adverse reaction in 3 patients and repeated local reaction in one patient resulting in withdrawing. Weekly mean of QoL showed a significant enhancement from 2.65 ± 1.92 [0; 9] (mean ± sd [min; max]) before starting treatment to 1.50 ± 1.27 [0;7] after the first injection of OMZ ($P > .001$). The improvement in quality of life remained statistically significant for all values of QoL scoring throughout the follow-up versus pre-treatment value ($P < .001$). There was no significant correlation between IgE level and the quality of life enhancement. QoL remained seasonal rhythmed although reduced all over the year by OMZ treatment.

Conclusion. Omalizumab injections appear to be a good option to enhance QoL and to reduce corneal complications in selected patients affected by VKC.

OA0029 | Triamcinolone acetonide aqueous (TAA) nasal spray improves ocular symptoms of seasonal allergic rhinitis sufferers (SAR): A meta-analysis

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Background: Ocular symptoms are equally and at times more frequently bothersome than nasal symptoms. Intranasal corticosteroids (INS) are a standard treatment of SAR and have positive effect

on ocular symptoms that is considered a class effect. TAA is an effective and safe INS for the treatment of allergic nasal symptoms and is expected to also exert therapeutic activity in the improvement of SAR ocular symptoms.

Method: The treatment impact of TAA 220 µg for SAR on ocular symptoms was assessed for the efficacy of improvement in the Sanofi® database. Selection criteria included randomized, single or double-blind, placebo-controlled and active-controlled with fluticasone propionate (FP) clinical trials that enrolled children ≥ 12 years of age and adults. The aim was to re-analyze the data of the selected clinical trials that collected ocular symptoms and perform a meta-analysis to estimate and identify the magnitude effect and clinical significance of TAA on total ocular symptoms and individual symptoms (tearing, itching and redness). The overall estimate of difference in mean change (Mean) between TAA and placebo or TAA and FP from baseline to week 2, at least, with standard error (SE), and associated 95% confidence interval (CI) was calculated using fixed effects model meta-analysis. The study was sponsored by Sanofi.

Results: Eight selected studies (n = 1679 patients) assessed ocular symptoms as secondary outcome. Four studies vs placebo with total ocular symptoms (n = 794); 2 studies vs placebo with individual symptoms (n = 242) and 2 studies vs FP with total ocular symptoms (n = 643).

TAA vs Placebo (n = 1036): All 6 studies that compared TAA vs placebo had data available at week 2. TAA demonstrated a positive treatment effect for total ocular symptoms [Mean −0.32 (0.061) 95%CI (−0.444 to −0.203)] and for tearing [Mean −0.21 (0.102) 95%CI (−0.411 to −0.011)]. There was no difference detected for redness or itching.

TAA vs Fluticasone (n = 643): TAA and FP were compared weekly over the course of 3 weeks of treatment. TAA produced similar improvement of total ocular symptom with no difference of treatment effect compared with FP at week 1: Mean 0.01 (0.062) 95%CI (−0.116 to 0.128), week 2: Mean −0.09 (0.068) 95%CI (−0.220 to 0.045) or week 3: Mean −0.07 (0.068) 95%CI (−0.203 to 0.063).

Conclusion: TAA was superior to placebo in improving tearing and total ocular symptoms and was equivalent to FP in improving total eye symptoms in SAR patients.

OA0030 | Efficacy of N-Acetyl Aspartyl Glutamic versus Fluorometholone 0.1 eye drops in subjects with moderate allergic conjunctivitis to birch pollen challenged in an environmental exposure chamber

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Background: Topical mast cell stabilizers are used for allergic conjunctivitis, but their efficacy as compared to topical corticosteroids is not known. We studied the efficacy of topical N-acetyl aspartyl glutamic acid 4.9% (NAAGA) versus fluorometholone 0.1% (FM) in subjects with moderate allergic conjunctivitis during controlled exposures to airborne Bet v1 in Strasbourg EEC.

Method: In this randomized, investigator-masked, cross-over, non-inferiority clinical study, 24 subjects with documented history of birch pollen allergic conjunctivitis were treated for 5 days with NAAGA or FM (one drop 4 times daily) and exposed to a fixed airborne concentration of birch pollen in the ALIATEC environmental exposure chamber (EEC). The primary endpoint was the quantity of birch pollen leading to conjunctival response (Abelson score ≥ 5). A linear model for cross-over studies was used to establish the non-inferiority of NAAGA versus FM with a margin of 0.5.

Results: The mean quantity of allergen responsible for conjunctival response was 1.30 ± 0.63 ng in subjects treated with NAAGA versus 1.32 ± 0.58 ng in subjects treated with FM. The hazard ratio of a positive conjunctival response was 0.977 (95%CI: 0.812; 1.174) demonstrating non-inferiority. The time to conjunctival response was 114.8 ± 55.0 min and 117.9 ± 73.2 min with NAAGA and FM, respectively. The mean symptom scores (itching and tearing) until the exit of the EEC were not different between groups (1.78 ± 1.22 versus 1.71 ± 1.04, respectively). In addition, NAAGA presented less adverse events than FM, including ocular adverse events.

Conclusion: The ALYATEC EEC is a good model to induce specific hypersensitivity to birch pollen. This study confirms the efficacy of NAAGA when compared to fluorometholone 0.1% in patients with moderate allergic conjunctivitis to birch pollen.

SUNDAY, 2 JUNE 2019
OAS 06
NOVEL TREATMENTS AND EPIDEMIOLOGY OF URTICARIA AND ANGIOEDEMA

OA0031 | Ligelizumab achieves sustained control of chronic spontaneous urticaria symptoms of hives, itch and angioedema: 1-year treatment results

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Background: Ligelizumab achieved greater control of symptoms of hives, itch and angioedema versus omalizumab and placebo in patients with chronic spontaneous urticaria (CSU) inadequately controlled with H1-antihistamines, alone or combined with H2-antihistamines and/or leukotriene receptor antagonists, up to Week 20 (last treatment at Week 16) in the core Phase 2b study (NCT02477332). Here, we report the efficacy and safety of ligelizumab 240 mg up to 1 year in an open-label, single-arm extension study (NCT02649218) in patients who completed the core study and presented with active disease (7-day Urticaria Activity Score [UAS7] ≥12).

Method: After washout of the last dose in the core study and evidence of disease activity, patients entering the extension study received ligelizumab 240 mg every 4 weeks (q4w) for 52 weeks; further monitoring for a 48-week follow-up is ongoing. Disease activity was assessed with the UAS7. Angioedema occurrence was recorded by patients in the Urticaria Patient Daily Diary starting 7 days before the baseline visit (i.e. the visit prior to first administration of ligelizumab in the extension study); at all other visits, it was reported for the previous 7 days.

Results: From the core study population, 70.6% (226/320) of patients entered the extension study, with 88.9% (201/226) completing 1 year of open-label treatment. Complete symptom control (UAS = 0) was achieved in 35.4% of patients after the first dose of ligelizumab (Week 4). Complete responses were sustained and over 50% of patients achieved UAS7 = 0 at the end of Week 52. Throughout the one-year treatment period, 75.8% of patients (95% confidence interval [69.9%, 81.3%]) cumulatively experienced complete symptom control at least once by the end of Week 52 based on the Kaplan-Meier method. Angioedema was reported by 33.2% of patients at baseline in the extension phase; this reduced to 10.8% at Week 4. Improvements in the proportion of patients reporting angioedema were sustained up to Week 52, at which time 93.0% of patients were angioedema-free. No new or unexpected safety signals were observed during 1-year of treatment in the extension study.

Conclusion: A high rate of early onset, complete control of hives and itch (UAS7 = 0), and angioedema was achieved and sustained with ligelizumab 240 mg q4w treatment for 52 weeks in patients with CSU inadequately controlled with standard of care including H1-antihistamines.

OA0032 | Ligelizumab is well tolerated and exhibits a safety profile similar to omalizumab and placebo in patients with chronic spontaneous urticaria

Sussman G[1]; Maurer M[2]; Giménez-Arnau AM[3]; Hua E[4]; Severin T[5]; Janocha R[5]

[1]University of Toronto, Toronto, Canada; [2]Charité—Universitätsmedizin Berlin, Berlin, Germany; [3]Hospital del Mar-IMIM, Universitat Autònoma Barcelona, Barcelona, Spain; [4]Shanghai Novartis Trading Ltd., Shanghai, China; [5]Novartis Pharma AG, Basel, Switzerland

Background: Ligelizumab is a next-generation high affinity humanized monoclonal anti-IgE antibody, which provides fast onset of action, sustained symptom control, as well as stronger efficacy compared with omalizumab in patients with chronic spontaneous urticaria (CSU). Here, we present the safety data from a Phase 2b study of ligelizumab in patients with CSU, whose symptoms remain uncontrolled with H_1-antihistamines alone or in combination with H_2-antihistamines and/or leukotriene receptor antagonists, and compare these with those of omalizumab and placebo.

Method: Adult patients with moderate to severe CSU (7-day Urticaria Activity Score ≥ 16) were randomized to receive subcutaneous ligelizumab 24, 72 or 240 mg, omalizumab 300 mg, or placebo every 4 weeks over 20 weeks (5 administrations). Safety was analyzed during 20 weeks of treatment and 24 weeks of follow-up.

Results: All tested doses of ligelizumab in this study were well tolerated and the safety profile was comparable with those of omalizumab and placebo. The most frequently reported adverse events (AEs; ≥10% in total) were viral upper respiratory tract infection (20.2%), upper respiratory tract infection (12.8%) and headache (11.3%). Viral upper respiratory tract infection AEs were more frequently reported in the placebo group (30.2%) than the ligelizumab (15.5% to 23.8%) or omalizumab (20.0%) groups. The proportion of AEs possibly related to treatment were 11.6%, 21.4% and 28.2% with ligelizumab 24, 72 and 240 mg, respectively compared with 8.2% for omalizumab and 27.9% for placebo. The higher rate seen with ligelizumab 72 and 240 mg vs. omalizumab was driven by injection site reactions (3.6% [72 mg], 5.9% [240 mg] vs. 0%) and injection site erythema (2.4% [72 mg], 4.7% [240 mg] vs. 0%). No meaningful differences among groups were observed in other

AEs possibly related to treatment. The majority of AEs were mild (39.8% in total) or moderate (30.6% in total) across the treatment groups. The incidence of severe AEs was higher in the placebo group (16.3%) than in the ligelizumab (3.5% to 9.3%) or the omalizumab (5.9%) groups. No serious AEs were considered related to ligelizumab treatment and no deaths or anaphylaxis were reported.

Conclusion: All tested doses of ligelizumab in this study were well tolerated. While numerical differences in AE frequencies were seen between ligelizumab treatment groups and omalizumab, in general the safety data for the two compounds appeared comparable and similar to that of placebo.

OA0033 | Clinical efficacy of interleukin-5 receptor alpha blocker benralizumab in the treatment of chronic idiopathic urticaria

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Background: Over 60% of chronic idiopathic urticaria (CIU) patients remain symptomatic despite treatment with 2nd-generation antihistamines. The introduction of omalizumab has resulted in further significant improvement of CIU management. However, some patients don't respond or only partially respond to omalizumab (that prevents IgE cross-linking) and many have recurrence of CIU after discontinuation indicating the need for further development of treatments that target alternative therapeutic pathways. This pilot study investigated the use of benralizumab, an interleukin-5 receptor-α blocker, for treatment of moderate to severe CIU.

Method: This single blinded, placebo run-in study enrolled 12 CIU subjects (F:M = 9:3) unresponsive to H1-anti-histamines. After consent, subjects meeting all inclusion/exclusion criteria were initially treated with placebo followed by 3 doses of benralizumab (30 mg SC q 4 wks). Treatment response was assessed by measuring weekly Urticaria Activity Score (UAS7); the Chronic Urticaria Quality of Life Questionnaire Score (CU-QoL) was completed at baseline, after placebo and after each benralizumab treatment. A generalized linear mixed model (SAS, Cary, NC) adjusting for severity and duration of disease among subjects was used to determine statistical significance. The UAS7 minimal detectable change (MDC) was determined using the Bland and Altman method (MDC = 1.96 × UAS7 standard deviation between baseline and placebo; a UAS7 MDC decrease of ~14 is considered clinically significant).

Results: CIU subject mean age and disease duration was 47 and 7 years, respectively. Mean UAS7 scores at baseline, post-placebo, and post-benralizumab were 33, 29, and 14, respectively ($P < .0001$); mean CU-QoL scores were 59, 56, and 43, respectively ($P = .004$). Nine subjects completed the study; 7 were responders (5/7 UAS7 = 0; 2/7 UAS7 ≤ 6) and 2 were non-responders. Three subjects (2 responders; 1 non-responder) dropped out of the study after the second dose (one due to personal issues, one lost to follow-up and one due to non-response). Two responders and two non-responders previously failed omalizumab. No adverse events due to treatment were identified.

Conclusion: Treatment of CIU with benralizumab versus placebo significantly improved disease severity and quality of life. These preliminary data indicate that benralizumab may be an effective treatment for CIU unresponsive to H1-antihistamines. Further investigation into the pathomechanism(s) of anti-IL5Ra antagonists in CIU is warranted.

OA0034 | Ligelizumab retreatment is highly effective in patients with chronic spontaneous urticaria

Maurer M[1]; Giménez-Arnau AM[2]; Sussman G[3]; Hua E[4]; Severin T[5]; Janocha R[5]

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Background: Previous data have shown that a high proportion of patients with chronic spontaneous urticaria (CSU) achieved complete symptom control with ligelizumab treatment. Here, we report the retreatment efficacy of ligelizumab 240 mg in an open-label, single-arm extension study (NCT02649218).

Method: In the core Phase 2b trial (NCT02477332), eligible adult patients with moderate to severe CSU (7-day Urticaria Activity Score [UAS7] ≥ 16) were randomised to receive subcutaneous ligelizumab 24, 72 or 240 mg, omalizumab 300 mg, or placebo every 4 weeks (q4w) over 20 weeks. Following the double-blind treatment period, patients entered a 24-week treatment-free period. After washout of the last dose in the core study (Week 32), patients with evidence of disease activity (UAS7 ≥ 12) were eligible to enter an open-label, single-arm (ligelizumab 240 mg q4w) extension study. Response after retreatment was assessed with the UAS7; results from the core study are shown for those patients that entered the extension study.

Results: Overall, 70.6% (226/320) of patients entered the extension study. Sustained efficacy (complete responder rates [proportion of patients achieving UAS7 = 0] and UAS7 change from baseline) was seen following 12 weeks retreatment with ligelizumab 240 mg q4w regardless of dose received during the core study (see Table 1). Similar trends were observed for complete responder rates for HSS7 = 0 and ISS7 = 0, as well as mean changes from baseline in HSS7 and ISS7.

Conclusion: Ligelizumab retreatment is highly effective in patients with chronic spontaneous urticaria, who have benefited from initial ligelizumab treatment and relapsed following treatment discontinuation.

TABLE 1. Intra-patient comparison between the core study Week 12 and extension study Week 12[a]

Core study treatment	UAS7 = 0 response rate (95% confidence interval)		UAS7 mean change from baseline (standard deviation)	
	Core study Week 12 (N = 51)	Extension Week 12 (N = 46)	Core study Week 12 (N = 51)	Extension Week 12 (N = 46)
Ligelizumab 72 mg	47.1% (32.9, 61.5)	52.9% (38.5, 67.1)	−21.6 (13.85)	−22.7 (13.74)
Ligelizumab 240 mg	45.7% (30.9, 61.0)	52.2% (36.9, 67.1)	−22.0 (13.65)	−21.7 (13.36)

[a] All patients enrolled in the extension study who received ligelizumab 240 mg q4w are included in this analysis

OA0035 | Anaphylaxis in patients with cold urticaria: Data from a mediterranean country

Fokoloros C; Pasali M.; Ntakoula M; Sandilos C; Chliva C; Aggelides X; Makris M

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Background: Cold urticaria is the second most common type of inducible urticaria, with an annual incidence of 0.05%. A significant proportion of patients experience anaphylactic reaction related to cold urticaria. This study presents the clinical data of these patients.

Method: Retrospective study of patients with clinical history of anaphylaxis due to cold urticaria who were evaluated in our Department during the past 4 years. The diagnosis was based on detailed confirmative clinical history while all patients underwent ice tube tests (ICT) and Tempest®4.0 (Peltier Thermostat) for identification of the temperature threshold.

Results: Sixty-five patients with confirmed cold urticaria were analyzed; 15/65 (23.1%) had an anaphylactic event (11/15 females; mean age 28 yrs, range 11-79 at disease onset). All (15/15, 100%) patients experienced anaphylaxis during aquatic activities. Surprisingly, only 6/15 (40%) reported symptoms at cold environment. None (0/15) of the patients used self-injectable epinephrine during anaphylaxis while all of them fully recovered within 30 minutes after re-warming. In 8/15 (53.3%) anaphylaxis was the first clinical manifestation of cold urticaria. Fourteen out of 15 (93.3%) had a positive ice tube test; 71.4% (10/14) with ice application ≤ 5 minutes, 21.4% (3/14) with ice application for 15 minutes. The patient who had negative ice tube test (in 15 minutes) reported one anaphylactic episode one year before and he was asymptomatic the last three months before his referral. Thirteen out of 15 patients underwent TempTest; 8/13 (61.5%) turned positive with mean threshold temperature 22.4°C (range: 14-27°C).

Conclusion: Patients with cold urticaria are at high risk of anaphylaxis; in Mediterranean countries, aquatic activities consist the most prevalent triggers. Patients with cold urticaria should always carry self-injectable epinephrine even if most episodes subside automatically.

OA0036 | Eczema and urticaria in the adult population in Portugal: A prevalence study

Carvalho DF[1]; Aguiar P[1]; Ferrinho P[2]; Mendes-Bastos P[3]; Palma-Carlos A[4]

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Background: Eczema and urticaria are both inflammatory skin diseases. The prevalence of both diseases varies worldwide and the reasons are unknown. We aimed to investigate the eczema and urticaria prevalence in the Portuguese adult (≥16 years old) population.

Method: A telephone interview survey was performed in the last quarter of 2017. To calculate the prevalences, subjects should have been previously diagnosed with eczema/urticaria by a health professional, be aged ≥ 16 years, and reside in Portugal. The sample had a proportion that was approximately representative by population, region, gender, and age group. Odds Ratios were performed to measure associations with prevalences. SPSS statistics and values of $P < .05$ with 95% confidence intervals were considered statistically significant.

Results: 5000 phone calls were analysed. The prevalence of eczema and urticaria in Portugal is 4.4% and 3.4%, respectively. Algarve is the region with the highest prevalence for both diseases. Being a female is the factor that most influenced these diseases with an OR = 1.99 [$P < .001$; CI 1.49-2.66] for eczema and 1.73 [$P = .001$; CI 1.25-2.40] for urticaria) with also, higher prevalences (5.7% and 4.2%, respectively).

Conclusion: The prevalences found are higher than in previous studies in Portugal and comparable to results from other countries. Regarding urticaria, there is no evidence of a concrete number for prevalence of all types of urticaria. Being female with eczema and urticaria is more common and represents a higher risk factor than male subjects.

TABLE

	Eczema, n = 220	OR (CI), *P* value	Urticaria, n = 168	OR (CI), *P* value	At least one of the diseases, n = 381	OR (CI), *P* value
Prevalence in adult population (CI %)	4.4% (3.8-5.0)		3.4% (2.9-3.9)		7.6% (6.9-8.4)	
Region, n (%) (CI %)						
North	60 (3.3) (2.8-3.8)	0.92 (0.50-1.70) *P* = .799	59 (3.2) (2.7-3.7)	1.05 (0.56-1.98) *P* = .874	115 (6.3) (5.6-7.0)	0.95 (0.60-1.48) *P* = .811
Centre	59 (5.0) (4.4-5.6)	1.42 (0.77-2.63) *P* = .261	36 (3.1) (2.6-3.6)	1.01 (0.52-1.97) *P* = .973	95 (8.1) (7.3-8.9)	1.24 (0.79-1.96) *P* = .355
Lisboa e Vale do Tejo	76 (5.5) (4.8-6.1)	1.51 (0.83-2.76) *P* = .178	52 (3.7) (3.2-4.3)	1.23 (0.65-2.34)	127 (9.1) (8.3-9.9)	1.39 (0.89-2.17) *P* = .148
Algarve	12 (5.3) (4.6-5.9)	1.51 (0.67-3.38) *P* = .316	9 (3.9) (3.4-4.5)	1.33 (0.55-3.21) *P* = .531	19 (8.3) (7.6-9.1)	1.30 (0.69-2.42) *P* = .416
Alentejo*	13 (3.4) (2.9-3.9)	1	12 (3.2) (2.7-3.6)		25 (6.6) (5.9-7.3)	1
P value+	.021		.861		.036	
Gender, n (%) (CI %)						
Female	149 (5.7) (5.0-6.3)	1.99 (1.49-2.66) *P* < .001	110 (4.2) (3.6-4.8)	1.73 (1.25-2.40) *P* = .001	252 (9.6) (8.8-10.4)	1.86 (1.49-2.32) *P* < .001
Male	71 (3.0) (2.5-3.5)	1	58 (2.4) (2.0-2.9)	1	129 (5.4) (4.8-6.0)	1
P value+	<.001		.001		<.001	
Age (years), n (%) (CI %)						
16-29	39 (7.4) (6.7-8.1)	2.85 (1.19-6.86) *P* = .019	13 (2.5) (2.0-2.9)	0.59 (0.25-1.40) *P* = .232	51 (9.7) (8.9-10.5)	1.57 (0.85-2.91) *P* = .151
30-49	86 (4.7) (4.1-5.3)	1.76 (0.76-4.09) *P* = .188	49 (2.7) (2.2-3.1)	0.63 (.305-1.31) *P* = .215	132 (7.2) (6.5-7.9)	1.13 (0.64-2.0) *P* = .668
50-79	89 (3.7) (3.1-4.2)	1.36 (0.58-3.14) *P* = .479	97 (4.0) (3.5-4.5)	0.95 (0.47-1.91) *P* = .884	184 (7.6) (6.8-8.3)	1.19 (0.68-2.10) *P* = .544
≥80*	6 (2.8) (2.3-3.2)	1	9 (4.1) (3.6-4.7)	1	14 (6.5) (5.8-7.1)	1
P value+	.001		.063		.255	
Prevalence in adult population (CI %)	4.4% (3.8-5.0)		3.4% (2.9-3.9)		7.6% (6.9-8.4)	
Region, n (%) (CI %)						
North	60 (3.3) (2.8-3.8)	0.92 (0.50-1.70) *P* = .799	59 (3.2) (2.7-3.7)	1.05 (0.56-1.98) *P* = .874	115 (6.3) (5.6-7.0)	0.95 (0.60-1.48) *P* = .811
Centre	59 (5.0) (4.4-5.6)	1.42 (0.77-2.63) *P* = .261	36 (3.1) (2.6-3.6)	1.01 (0.52-1.97) *P* = .973	95 (8.1) (7.3-8.9)	1.24 (0.79-1.96) *P* = .355
Lisboa e Vale do Tejo	76 (5.5) (4.8-6.1)	1.51 (0.83-2.76) *P* = .178	52 (3.7) (3.2-4.3)	1.23 (0.65-2.34)	127 (9.1) (8.3-9.9)	1.39 (0.89-2.17) *P* = .148
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Alentejo*	13 (3.4) (2.9-3.9)	1	12 (3.2) (2.7-3.6)		25 (6.6) (5.9-7.3)	1
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Male	71 (3.0) (2.5-3.5)	1	58 (2.4) (2.0-2.9)	1	129 (5.4) (4.8-6.0)	1
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16-29	39 (7.4) (6.7-8.1)	2.85 (1.19-6.86) *P* = .019	13 (2.5) (2.0-2.9)	0.59 (0.25-1.40) *P* = .232	51 (9.7) (8.9-10.5)	1.57 (0.85-2.91) *P* = .151

(Continues)

TABLE continued

	Eczema, n = 220	OR (CI), *P* value	Urticaria, n = 168	OR (CI), *P* value	At least one of the diseases, n = 381	OR (CI), *P* value
30-49	86 (4.7) (4.1-5.3)	1.76 (0.76-4.09) *P* = .188	49 (2.7) (2.2-3.1)	0.63 (.305-1.31) *P* = .215	132 (7.2) (6.5-7.9)	1.13 (0.64-2.0) *P* = .668
50-79	89 (3.7) (3.1-4.2)	1.36 (0.58-3.14) *P* = .479	97 (4.0) (3.5-4.5)	0.95 (0.47-1.91) *P* = .884	184 (7.6) (6.8-8.3)	1.19 (0.68-2.10) *P* = .544
≥80*	6 (2.8) (2.3-3.2)	1	9 (4.1) (3.6-4.7)	1	14 (6.5) (5.8-7.1)	1
P value+	.001		.063		.255	

* Reference category.
+ chi-square test.

SUNDAY, 2 JUNE 2019
OAS 07
TAILORED ASTHMA TREATMENT

OA0037 | Ketorolac nasal challenge and aspirin treatment in patients with aspirin-exacerbated respiratory disease

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Background: Oral aspirin challenge is the gold standard for the diagnosis of AERD, but it puts the patient at high risk of severe reactions. Aspirin desensitization and extended aspirin therapy has been proved to be effective in improving asthma and sinonasal symptoms in AERD. Objective: 1) To evaluate the diagnostic accuracy and safety of ketorolac nasal provocative challenge (KNC) in patients suspicious of AERD using an acoustic rhinometer; 2) to determine the desensitization clinical outcome and the results of short-term treatment with aspirin in patients suffering from AERD.

Method: Thirty-two patients with suspected AERD underwent KNC using an acoustic rhinometer. We considered the challenge as positive if both an increase of 30% or more of the nasal symptoms recorded by a visual analogical scale and a drop of 30% in the sum of the nasal cavities' volume –ranging from 2 to 8 cm- were achieved. Patients with negative results were provided with 500 mg of aspirin, whereas those with positive results underwent a nasal/oral desensitization procedure with ketorolac/aspirin and they were also treated with aspirin during 3 months. Three questionnaires and an olphatometric test were used to evaluate the clinical outcome to aspirin treatment.

Results: Twenty patients showed a positive response to NKC. All patients displayed a nasoocular reaction; four of them showed also mild asthma exacerbation. No patient with negative results in KNC reacted to the oral challenge with aspirin. Desensitization status was achieved in 14 patients without any significant reactions. All questionnaire scores showed a significant clinical improvement of asthma and sinonasal symptoms within 30 days from the start of treatment.

Conclusion: KNC using an acoustic rhinometer is safe and accurate; it has an excellent negative predictive value in AERD diagnostic. Nasal/oral ketorolac/aspirin desensitization is a safe method for aspirin introduction in patients with AERD. The aspirin therapy early improves asthma control, sinonasal symptoms and quality of life in patients with AERD.

OA0038 | Young patients with asthma can generate sufficient inspiratory flows via an easy-to-use dry powder inhaler (DPI) delivering salmeterol/fluticasone propionate and budesonide/formoterol treatments

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Background: Asthma prevalence is rising in children and adolescents and it has become the most common chronic disease among children. New treatment options for effective and safe management of asthma in children and adolescents are therefore urgently needed. To ensure consistent dose delivery of the drug from a DPI the peak inspiratory flow (PIF) should be 30 l/min or higher. We evaluated if young patients can achieve sufficient inspiratory flows for effective use of recently approved Easyhaler medium-to-high resistance combination DPI devices for salmeterol/fluticasone propionate and budesonide/formoterol.

Method: Two randomized, multicenter, crossover open-label studies assessed PIF rates via Easyhaler DPI in patients with asthma. After practicing, three inspiratory flow curves were recorded through the inhaler connected to a pneumotachograph. The highest value was analyzed. The PIF was the primary variable, and inspiratory volume recorded at the same time was the secondary variable.

Results: 287 subjects 6-88 years of age with documented diagnosis of asthma of various severities were included in the studies. 35.5% of the patients were below 18 years of age and 39.4 % were male. The mean PIF rate (SD) was 66.7 (13.4) l/min. There was a moderate correlation of age, height and weight with PIF (0.373, 0.348, and 0.349, respectively, $P < .001$ for all) in children younger than 12 years (n = 92). For adolescents and adults, there was no significant correlation between age and PIF. However, already the patient group of 9-17 years (n = 61) reached the similar mean PIF rate level with adults (64.5 (9.3) l/min vs. 67.0 (13.9) l/min) whereas children below 9 years had mean PIF rate of 56.8 (13.0) l/min. In addition, in patients below 18 years of age all but one patient achieved PIF higher than 30 l/min which is required to ensure consistent dose delivery from the DPI. The mean (SD) inspiratory volume was 1.55 (0.5) in patients below 18 years of age and 2.14 (0.7) in adults.

Conclusion: Young patients with asthma achieve inspiratory flows sufficient for effective use of Easyhaler DPI.

OA0039 | Dupilumab effect on asthma control and health-related quality of life in patients with oral corticosteroid-dependent severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps

Castro M[1]; Rabe KF[2]; Brusselle G[3]; Rice MS[4]; Rowe P[5]; Deniz Y[6]; Kamat S[6]; Khan A[7]

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Background: Dupilumab (DPL), a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. DPL is approved for treatment of inadequately controlled, moderate-to-severe atopic dermatitis and, in the USA, for patients (pts) aged ≥ 12 years with moderate-to-severe eosinophilic or oral corticosteroid (OCS)-dependent asthma. In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), in pts with OCS-dependent, severe asthma, add-on DPL 300 mg every 2 weeks vs placebo (PBO) reduced OCS dose and severe asthma exacerbations and improved FEV_1, independently of baseline (BL) eosinophil levels, and was generally well tolerated; 5-item Asthma Control Questionnaire (ACQ-5; least squares [LS] mean difference −0.47) and 7-item Asthma Quality of Life Questionnaire (AQLQ) scores (LS mean difference 0.35) were also improved. This analysis assessed DPL effect on asthma control and health-related quality of life (HRQoL) in OCS-dependent, severe asthma pts with comorbid chronic rhinosinusitis with and without nasal polyps (CRSwNP/CRSsNP) and without chronic rhinosinusitis or nasal polyps (non-CRS/NP).

Method: Asthma control/HRQoL were assessed by ACQ-5 (range 0–6) and AQLQ (range 1–7) with higher scores indicating less asthma control and better HRQoL, respectively. A change in total score of ≥ 0.5 was considered clinically meaningful on both. Change from BL at Week 24 in both scores was analyzed using mixed-effect models with repeated measures.

Results: 72/210 pts self-reported medical history of CRSwNP/CRSsNP. These pts had higher BL FEV_1 and comparable eosinophil counts, FeNO levels, ACQ-5 and AQLQ scores vs non-CRS/NP pts. At Week 24, DPL reduced ACQ-5 scores by LS mean —1.15 (LS mean difference vs PBO —0.75; P = .006) in CRSwNP/CRSsNP pts and by −1.00 (LS mean difference vs PBO −0.35; P = .06) in non-CRS/NP pts. AQLQ scores in the DPL group improved by 0.91 (LS mean difference vs PBO 0.49; P = .06) in CRSwNP/CRSsNP pts and by 0.88 (LS mean difference vs PBO 0.29; P = .07) in non-CRS/NP pts. Overall, the most frequent TEAE in DPL vs PBO pts was eosinophilia, occurring in 14% vs 1% pts (no clinical consequences). Injection-site reactions occurred in 9% of DPL vs 4% of PBO pts.

Conclusion: Dupilumab vs PBO showed trends of improvement in asthma control and HRQoL, despite reduction in OCS dose, in OCS-dependent, severe asthma pts with comorbid CRSwNP/CRSsNP and non-CRS/NP, and was generally well tolerated.

OA0040 | Increasing aeroallergen sensitization predicts response to omalizumab therapy during the fall season among children with persistent asthma

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Background: Aeroallergen sensitization has been associated with increased asthma morbidity and is included in the indication for treatment with omalizumab in uncontrolled asthma. This study sought to investigate the predictive relationship between aeroallergen sensitization profiles in children with asthma and their response to omalizumab treatment during the fall season.

Method: This is a retrospective analysis of patients aged 6 to 20 years who comprised the control groups and the omalizumab-treated groups in two completed randomized clinical trials for inner-city children with asthma from the Inner-City Asthma Consortium. This analysis investigated if the overall number of aeroallergen sensitizations, defined by positive skin and/or blood tests, in an individual was associated with differential responses to fall treatment with omalizumab. The primary outcome was fall asthma exacerbations; the secondary outcome was the Composite Asthma Severity Index (CASI).

Results: The analysis included 761 patients with 62% male, 61% African American, and a median age of 10 years. Within the control group, there was a significant association between overall number of aeroallergen sensitizations and the risk of a fall asthma exacerbation (OR = 1.31, 95% CI 1.09-1.58, P < .01); however, there was no significant association between number of aeroallergen sensitizations and fall asthma exacerbations in the omalizumab-treated children (OR = 1.08, 95% CI 0.92–1.28, P = .36) indicating a significant subgroup (P < .01). Likewise, there was a significant association between overall number of aeroallergen sensitizations and the fall CASI outcome in the control group (β = .23, 95% CI = 0.02–0.44, P = .03), but not in the omalizumab-treated children (β = .07, 95% CI = −0.09 to 0.22, P = .41) indicating a significant subgroup (P = .03).

Conclusion: An overall greater number of aeroallergen sensitizations was associated with increasing asthma morbidity in control subjects, but not in omalizumab-treated children. Further studies are warranted to investigate if omalizumab therapy should be preferentially directed towards children with the greatest number of aeroallergens sensitizations.

OA0041 | Prevalence of fungal-sensitization and response to mepolizumab in patients with severe eosinophilic asthma

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Background: Mepolizumab reduces exacerbation rates and corticosteroid use in patients with severe eosinophilic asthma (SEA). This post hoc analysis of the MENSA study assessed the prevalence of immunoglobulin E (IgE) fungal sensitization in patients with SEA and their response to mepolizumab.

Method: Patients aged ≥ 12 years with SEA were randomized to subcutaneous mepolizumab 100 mg (n = 194), intravenous mepolizumab 75 mg (n = 191), or placebo (n = 191) every 4 weeks for 32 weeks. Endpoints included prevalence of sensitization to a panel of fungal and aeroallergens; rate of clinically significant exacerbations; change from baseline in pre-bronchodilator forced expiratory volume in 1s (FEV_1); and blood eosinophil count (BEC) at Week 32.

Results: Overall, 51, 167, and 131 patients were IgE-sensitized to fungal allergen only, aeroallergen only, and both, respectively. Those sensitized only to fungal allergen had a lower baseline FEV_1. Baseline mean total IgE was higher in the fungal plus aeroallergen sensitized subgroup versus other subgroups (533.5U/mL vs. 63.2–274.51U/mL; $P < .001$ all). Reductions in clinically significant exacerbation rates with mepolizumab versus placebo were similar across allergen sensitization subgroups; however, patients sensitized to *Aspergillus fumigatus* and/or *Penicillium chrysogenum* showed a greater reduction. At Week 32, mepolizumab versus placebo increased FEV_1 from baseline by 95–129 mL in all subgroups, except those with only fungal sensitization. Mepolizumab reduced BEC from baseline by 80%–87% versus placebo across all subgroups.

Conclusion: In patients with SEA, mepolizumab reduced exacerbation frequency and BEC regardless of fungal or other allergen sensitization, with more pronounced reductions in patients sensitized to *A. fumigatus* and/or *P. chrysogenum*.

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OA0042 | Change in post-bronchodilator FEV_1 for patients with severe asthma with eosinophilic features following benralizumab therapy

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Background: Benralizumab, an interleukin-5 receptor alpha–directed cytolytic monoclonal antibody, uniquely depletes blood and tissue eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity. We examined whether benralizumab improves post-bronchodilator lung function for patient subgroups with severe asthma and eosinophilic features.

Method: We assessed post-bronchodilator FEV_1 (post-FEV_1) for at-risk subgroups in a *post-hoc* analysis of pooled data from the Phase III SIROCCO (48 weeks; NCT01928771) and CALIMA (56 weeks; NCT01914757) trials. Subgroups were defined by previously identified predictors of enhanced benralizumab response: ≥3 exacerbations in prior year, baseline pre-bronchodilator forced vital capacity < 65% of predicted (FVC < 65%), adult-onset disease, and nasal polyposis. Subgroups were further classified by blood eosinophil counts (<300 vs. ≥300 cells/μL). All *P*-values were nominal.

Results: Improvements in post-FEV_1 for patients with ≥ 3 exacerbations in prior year, FVC < 65%, adult-onset disease, or nasal polyposis were greater with benralizumab than placebo (by 170, 230, 150, and 330 mL, respectively; all $P < .0001$). Patients with blood eosinophil counts ≥ 300 cells/μL and ≥ 3 exacerbations in prior year, FVC < 65%, adult-onset disease, or nasal polyposis had greater improvements with benralizumab than placebo (by 190, 270, 180, and 310 mL, respectively; all $P < .005$). Post-FEV_1 also improved with benralizumab vs. placebo for patients with blood eosinophil counts < 300 cells/μL and ≥ 3 exacerbations in prior year (140 mL) or nasal polyposis (340 mL; both $P < .05$).

Conclusion: At-risk patients with frequent exacerbation, poor baseline lung function, adult-onset disease, or nasal polyps who were treated with benralizumab had more clinically meaningfully improvements in post-FEV_1 than those who received placebo. For these first three subgroups, the difference was more pronounced for patients with blood eosinophil counts ≥ 300 cells/μL. Although further investigation is needed, our data suggest that patients with these predictors and greater eosinophilic burdens may have improvements in airway physiology or remodeling following benralizumab treatment.

SUNDAY, 2 JUNE 2019
OAS 08
PEDIATRIC CUTANEOUS DISEASES AND DRUG ALLERGY

OA0043 | Impact of different definitions of atopic dermatitis on phenotyping the long-term course of the disease

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Background: There is no universally accepted definition of atopic dermatitis (AD) in epidemiological studies. We aimed to investigate the impact of different definitions of AD on phenotyping the long-term course of the disease.

Method: In an unselected birth cohort, 1184 participants were recruited prenatally and followed prospectively. Participants attended clinical follow-ups at ages 1, 3, 5, 8 and 11 years, when the current parentally-reported AD (PRAD) and regular topical treatment use were ascertained using interviewer-administered questionnaires. Data from primary care medical records including the doctor diagnosis of AD (DDAD) were extracted for 922 children. We defined the annual prevalence of current AD using three different definitions: (1) PRAD; (2) DDAD; and (3) the composite definition (CDAD) comprising at least two of the three features (PRAD, DDAD, and regular use of topical corticosteroids and/or moisturisers). Using latent class analysis (LCA), we determined the profiles (phenotypes) of the long-term course of AD using the three definitions. To assess the impact of different definitions on the obtained latent classes, we compared the proportion of children moving between phenotypes.

Results: In all definitions, the annual prevalence of AD declined steadily from age 1 to 11 years: 36% to 16% (PRAD), 47% to 6% (DDAD), and 28% to 6% (CDAD). For PRAD, LCA identified four classes (phenotypes): "No AD" (58%); "Early-onset persistent" (11%)"; "Early-onset remitting" (21%)"; and "Late-onset" AD (10%). For DDAD and CDAD, the optimal number of phenotypes was three: "No AD (66% and 74% respectively)"; "Early-onset persistent" (8% and 6%)"; and "Relapsing-remitting" (26% and 19%)". Posterior probabilities of class membership were generally high, with only 70 (6.5%), 22 (2.4%), and 43 (4.3%) children having low membership probability (<0.60) of any phenotype in models using PRAD, DDAD, and CDAD, respectively. However, although AD phenotypes at a population level appeared similar when different definitions were used, a considerable proportion of children (n = 485, 45%) moved between phenotypes. For example, amongst children assigned to "Early onset persistent" using PRAD, only 26% and 38% remained in the same phenotype in DDAD and CDAD models.

Conclusion: The use of different definitions of AD has a major influence on the number and type of AD phenotypes identified by the longitudinal LCA, as well as the individual phenotype membership.

OA0044 | Food allergens in skin care products marketed for children

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Background: Cosmetics marketed for children are commonly perceived as harmless and products that claim to be natural are portrayed to be superior. It has been known that topical food allergen application can cause percutaneous sensitization and symptoms in allergic individuals. There is a lack of knowledge on the occurrence of food allergens in cosmetics intended for children. The objective of this study was to analyze the prevalence of common food allergens in skin care products marketed for children and to examine its association with cosmetic label claims.

Method: Ingredients of skin care products intended for use in babies and children were analyzed for prevalence of common food allergens: milk, eggs, wheat, soya, tree nuts, peanuts and sesame. Products were categorized according to their purpose and label claims (natural, ecological, dermatologically tested, hypoallergenic, for sensitive skin, or none). Products intended to treat specific conditions (rash ointments, emollients, etc.) were excluded.

Results: 207 skin care products were analyzed. Most products were manufactured in European countries other than Lithuania (95.2%), minority were manufactured locally (4.8%). Among analyzed cosmetics: 59.9 % contained no food allergens, 26.6 % contained one, 12.1 % two and 1.4 % contained three food allergens. Within the products that contained food allergens: 42.5% contained almond, 24.8% wheat, 15% soya, 10.6% sesame, 5.3% oats and 1.8% contained milk. No products containing peanut, eggs, or tree nuts other than almond were found. No significant difference in prevalence of food allergens was found between products produced in Lithuania compared to other countries. Skin care products that claimed to be natural or ecological contained at least one food allergen significantly more often than products that claimed to be intended for sensitive skin, hypoallergenic, dermatologically tested or had no claims at all (P = .001).

Conclusion: Food allergens are prevalent in children's cosmetics, the most common ones being almond, wheat and soya. Products claiming to be natural or ecologic contain food allergens more often than others. When allergic reactions from topical allergen application or percutaneous sensitization are of concern, advising parents to carefully read cosmetics ingredients lists, disregarding label claims, seems like a reasonable advice.

OA0045 | The efficacy and safety of the up-dosing of second-generation H1 antihistamine in treatment of chronic spontaneous urticaria in a paediatric population

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Background: The first line treatment of chronic spontaneous urticaria (CSU) is represented by second-generation H1 antihistamines (SGH1), that may be increased up to four times the permitted dose in case of lack of response. Consensus guidelines on treatment of CSU in adults are applied also in children, but there is a limited knowledge on the safety and efficacy of SGH1 up-dosing in pediatric age. The aim of this study was to evaluate the efficacy and safety of the up-dosing of SGH1 in a paediatrics population with CSU.

Method: We retrospectively reviewed the electronic charts of patients referred to our Allergy Unit from January 2017 to November 2018 for CSU, defined by the presence of wheals, angioedema or both for ≥ 6 weeks. The demographic characteristics, underlying diseases, responses to standard or increased doses of SGH1 and its side effects were recorded. Patients who did not respond to 4 doses of SGH1, or worsened after 3 doses, were treated with anti-IgE monoclonal antibodies.

Results: A total of 44 children [mean age (±standard deviation, SD): 9.25 ±4.33 years] with CSU were collected: 19/44 (43.2%) patients responded to the standard dose of SGH1 and the mean time of treatment was of 7.1 ± 6.5 months; 14/44 (29.5 %) patients required a double dose of SGH1 in a mean time of 9.93 ± 5.86 months; 1/44 (2.3%) and 2/44 (4.5%) patients recovered with the threefold and the fourfold dose of SGH1 respectively. Three and five children who did not respond to fourfold and threefold doses of SGH1, respectively, were treated with anti-IgE monoclonal antibody for a total of 8/44 (18.2%) patients. Seven out of 44 (15.9%) patients experienced side effects with SGH1: 3 patients during the treatment with standard dose, 2 patients at the double dose and 2 at the threefold dose. The most frequent side effect was somnolence (4/7, 57.1%);one patient complained of headache, one complained of dizziness and the other enuresis.

Conclusion: This is the first study investigating the efficacy and safety of the up-dosing of SGH1 for CSU in a so high number of children. According to our results, SGH1 resulted well tolerated with few and mild side effects even when used in up-dosing. Anyway, the efficacy of SGH1 is not proportional to the dose administered, most (29.5 %) of the children recovered after doubling the dose of SGH1, with very poor response to three (2.3 %) or four times (4,5%) the standard dose of SGH1.

OA0046 | Aetiopathogenesis of severe cutaneous adverse reactions (SCARS) in children: A 9-year experience in a tertiary-care paediatric hospital setting

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Background: Severe cutaneous adverse reactions (SCARs) are a group of delayed-type hypersensitivity reactions to drugs. SCARS are potentially life threatening, and associated with various clinical patterns: drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). So far, incidence, potential triggers and management of SCARS have not been investigated in large-scale epidemiological studies on children. The aim of our study was to collect epidemiological, clinical and aetiological data from children with SCARs referred to the tertiary-care paediatric hospital of Anna Meyer in Florence.

Method: From January 2010 to December 2018, charts of children with a diagnosis of SCAR were both retrospectively and prospectively reviewed and data collected during the acute phase and/or during subsequent allergy evaluation at least one month after resolution of the symptoms and withdrawal of corticosteroids (CCS). Patients referred to our Allergy Unit, underwent patch and intradermal tests with the culprit drug according to the European Network for Drug Allergy (ENDA) guidelines. Reactions to amoxicillin clavulanic-acid or carbamazepine were also investigated by in vitro lymphocyte transformation tests. All children were tested for possible concomitant infectious diseases.

Results: The total incidence of SCARs in hospitalised children was 0.33% over a 9 years period. Fifty-two children were enrolled (31 M; 21 F; mean age 8.9 years): 17/52 (32.7%) cases of DRESS, 30/52 (57.7%) SJS, 3/52 (5.8%) TEN, 2/52 (3.8%) AGEP. Mean latency from drug exposure and onset of symptoms was 9.35 days. Twelve out of 52 SCARs (23%) were caused by infectious agents. Twenty-six out of 52 (60%) patients underwent drug allergy investigations and 50% of them resulted positive. Combining clinical history and results of allergy work-up, 73.1% SCARs were caused by drugs. The 3.8% SCARS remained idiopathic. CSS were most frequently used to treat both DRESS (64.7%) and SJS/TEN (66.6%) cases. AGEP cases spontaneously recovered after a prompt drug withdrawal. No deaths occurred.

Conclusion: In this study, SCARs incidence is in line with data reported in the literature. Drugs were most commonly the leading cause of SCARs. Management of SCARs required cooperation among the various professional figures for an early diagnosis and a prompt treatment. The mortality rate seems to be lower in children than in adults.

OA0047 | Evaluation of hypersensitivity reactions to cancer chemotherapeutic agents in childhood

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Background: In the past decade with the increasing use of chemotherapeutic agents for neoplastic disease, hypersensitivity reactions (HSRs) have been increasingly documented. The aim of this study was to investigate the frequency, clinical features and management strategies of HSRs due to chemotherapeutics agents in childhood.

Method: Between January 2007 and December 2018, the patients who were treated for neoplastic diseases in the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital were evaluated. Patients who developed a HSR to chemotherapeutic agent were included in the study.

Results: Forty five patients were included of which 55,6% had experienced anaphylaxis. 32 (71,1%) had reaction with *E.coli*-asparaginase. The other agents were polyethylene glycol (PEG)-asparaginase 4,5% (n = 2), etoposide 13,3% (n = 6), methotrexate 6,7% (n = 3), carboplatin 2,2% (n = 1) and procarbazine 2,2% (n = 1). Of the 32 patients who had reaction with *E.coli*-asparaginase, treatment was continued with PEG-asparaginase in 11 and *Erwinia* asparaginase in 17 patients. 3 patients had the drug with desensitization. Of the 11 patients who had PEG-asparaginase, 4 developed a reaction and 3 continued the treatment with *Erwinia* asparaginase but one of these had anaphylaxis. Two patients had a reaction with PEG-asparaginase at the beginning and they continued their treatment with *Erwinia* asparaginase.

Of the patients with etoposide hypersensitivity (n = 6), 66,7% had anaphylaxis. Two of them had the drug with desensitization and 2 of them had the drug with premedication and prolonged infusion.

2 patients had anaphylaxis to methotrexate. Of the patients procarbazine and carboplatin hypersensitivity, none of them had anaphylaxis. Procarbazine was given with premedication. Carboplatin was discontinued.

Conclusion: Although all chemotherapeutic agents can cause HSRs, asparaginase is the most common agent in children. Most of reactions are immediate type. Many of the patients can take their treatment by drug replacement or desensitization.

OA0048 | Negative predictive value of five-day drug provocation test for non-immediate beta-lactam allergy in children

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Background: Oral provocation test (OPT) is the gold standard in the diagnosis of drug allergies. In recent years, extending the provocation period by continuing the test at home is recommended for patients with suspected delayed beta-lactam reactions and negative OPT. Prolonged provocation time can be 2-10 days, there isn't a consensus for the time period.

Method: The families of children with suspected non-immediate beta-lactam allergy who underwent 5-day drug provocation test at home after negative OPT between January 1, 2013, and December 31, 2017, were questioned with telephone interviews about re-exposure to tested drug. Patients whose reported reactions during re-exposure were re-evaluated

Results: A total of 355 patients with suspected non-immediate beta-lactam allergy had negative results in the 5-day provocation test. The median age at provocation was 4.2 years (interquartile range: 1.98-7.02 years) and 52.9% were male. In this group, 295 (83.4%) had history of reaction to penicillin and 60 (16.6%) to cephalosporin. The families of 255 patients (72%) could be contacted. Of these 255 patients, 179 (70%) had used the same drug and 6 (3.4%) of these cases declared that they had reactions. These 6 patients were re-evaluated in the allergy clinic. Five of these patients had had underwent OPT with amoxicillin clavulanate and one with cefixime. When detailed history was taken, it was realised that 2 of 5 patients amoxicillin clavulanate reaction, used the drug unintendedly after their reaction with re-exposure and did not have any symptoms. One of the patients underwent allergy workup and tested negative, the other two refused the test. The patient with reported cefixime reaction underwent repeated provocation and tolerated the drug. Therefore the negative predictive value of 5-day prolonged provocation test was 98.9%.

Conclusion: The 5-day prolonged drug provocation test has high negative predictive value and seems appropriate in duration for children with suspected non-immediate beta-lactam allergy.

SUNDAY, 2 JUNE 2019

OAS 09

DAMAGING EFFECTS OF AIR POLLUTANTS AND CLIMATE CHANGE

OA0049 | Effects of air pollutants on pulmonary function in children monitoring by mobile phone application

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Background: The acute effects of air pollutants on asthma remain unclear. This study investigated the acute effects of ambient air pollution on pulmonary function among asthma in children by mobile health applications.

Method: We designed a smartphone app to provide timely support to patients with asthma. Peak expiratory flow (PEF) recordings were made twice daily and were corrected by age and gender. The severity of asthma by GINA guideline and asthma control test (ACT) test score were also monitored for 4 months. Ambient air pollution parameters of particulate matter (PM), ozone (O3), oxides of nitrogen (NO2),carbon monoxide (CO), and sulfur dioxide (SO2) were measured from air monitoring station at each time while PEF recordings by linking to Global Positioning System. Effects of exposure to pollutants on self-measured PEF and ACT scores were assessed in 186 person- days of observations.

Results: The mean values of PEF were 249.09 ± 68.59 L/min. In models adjusted for age, gender, season, daily average temperature and relative humidity, an increase of 10-unit of mean concentrations of PM2.5, PM10, NO2, and SO2 was associated with a decrease in PEF of 8.40 L/min (95% CI 2.39, 14.40), 4.64 L/min (95% CI 1.17, 8.11), 8.54 L/min (95% CI 0.64, 16.43), and 57.90 L/min (95% CI 8.17, 107.62), respectively. The decrease in ACT score was associated with air pollutant concentrations.

Conclusion: Increases in air pollutant concentrations has acute effects on the pulmonary function. Exposure to air pollution can lead to decrease asthma control in children.

OA0050 | Modification of effect between air pollution and lung function by the inflammatory potential of diet: A cross-sectional study in children

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Background: Inhalation of fine particulate matter (PM) can cause systematic inflammation and oxidative stress, which may further aggravate the development and progression of asthma. Although nutritional intake of fatty acids and antioxidants may attenuate some effects of fine particulate matter (PM), the role of overall dietary intake has not been studied. Therefore, we aimed to investigate the modification of the association between air pollution and childhood asthma-related outcomes by the effect of the inflammatory potential of diet.

Method: In a cross-sectional study, 501 (48.1% males, aged 7 to 12 years) of 858 children attending 71 classrooms from 20 local schools were selected. Spirometry and airway reversibility, exhaled level of nitric oxide, skin-prick testing and current symptoms (breathing difficulties and irritative cough) were assessed. Asthma was defined based on self-reported medical diagnosis and currently under anti-asthma medication. Dietary inflammatory potential was evaluated by the Dietary Inflammatory Index (DII) and calculated from a 24-hour dietary recall. Indoor air quality measurements were conducted in 20 schools and 71 classrooms for one week. The proportion of effects explained by the exposures to PM2.5 and PM10 were measured by generalized linear mixed model.

Results: After adjustments for age, sex, body mass categories according to US Centres for Disease Control (CDC) and exposure to tobacco at home, a more inflammatory diet increased the risk of children with asthma for PM2.5 (OR = 1.67, 95% CI 1.03, 2.73) and PM10 (OR = 1.75, 95% CI 1.07, 2.87) levels. Considering the inflammatory potential of diet in the exposure to PM2.5 and PM10, the risk of asthma increased in parallel with the DII, being statistically significant for children with asthma (OR = 0.89, 95% CI 0.81, 0.97 and OR = 0.92, 95% CI 0.87, 0.97).

Conclusion: These findings provide further support to the role of diet's inflammatory characteristics modulating the effects of indoor air pollution on lung function, highlighting the importance of children's diet as a potential solution to reduce the risk of asthma due to air pollution.

OA0051 | Climate change and air pollution their impact on atopic dermatitis patients

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Background: Climate change and, in particular, with global warming leading to a tropicalization of weather, are adding to the bad effects of air pollution on the skin atopic diseases.

Method: Sixty AD patients with 5 years or older from the Southern Italy Region, Campania, Italy, have been followed for 18 months between July 2017 and December 2018. Symptoms score including itching, sleep disturbance, erythema, dry skin, oozing, and edema, obtained by SCORAD ("SCORing Atopic Dermatitis") score. The effect of meteorological variables including daily mean temperature, relative humidity (RH), diurnal temperature range (DTR), rainfall and air pollutants including particulate matter with an aerodynamic diameter ≤ 10 μm (PM10), nitrogen dioxide (NO2), tropospheric ozone (O3) and total pollens count (TPC) on AD symptoms were elaborated using a generalized linear mixed model with adjustment for related confounding factors .

Results: The risk of AD symptoms increased by 222.7% (95% CI: 68.4, 782.4) according to a 5°C increase in DTR when it was > 14°C. An increase in PM_{10}, NO_2, O_3 and TPC by 1 Log 10 increased the risk of AD symptoms on the same day by 3.0%, 5.0%, and 5.9% , 4,5%, respectively. A 5°C increase in outdoor temperature and a 5% increase in outdoor RH was associated with 14% and 4.0% decrease in AD symptoms, respectively, on the same day. An increase of rainfall by 5 mm increased of SCORAD by 9% for the days with < 40 mm rainfall.

Conclusion: Climate change and air pollution are associated with AD symptoms in young and adult patients. Forecast of weather and air pollutants including particulate matter PM10, NO2, O3, and total pollens counts are important in management of atopic dermatitis patients.

OA0052 | Does air pollution affect pollen concentrations through radiative feedback in the atmosphere?

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Background: During periods with high air pollution and high amounts of aeroallergens, sensitive individuals may be co-exposed to a health damaging cocktail of atmospheric particles. High concentrations of particulate matter (PM) are known to affect the radiation balance and atmospheric dynamics, hence affecting the co-exposure of pollen and pollutants. Forecast models typically do not take this effect into account, potentially affecting calculated exposure levels.

Method: We explore the effect of radiative feedback from particulate matter on concentrations of aeroallergens by applying a newly developed model. The model is an extension of the atmospheric model WRF-Chem, where we have extended a parameterization originally designed for PM and dust. The extension covers common aeroallergens such as oak (*Quercus sp*), birch (*Betula sp*) and ragweed (*Ambrosia artemisiifolia*). We use the model to study a known air pollution event in early April 2014 over Northern Europe by making two model calculations, each containing both Saharan dust, anthropogenic PM and birch pollen: one with and one without radiative feedback. The model results from the two scenarios are compared through maps over Northern Europe, available observations of aeroallergens and statistical tests for significance. Finally, we evaluate the performance of the model's ability to predict plumes originating from countries to the South and East of the UK.

Results: During the Saharan dust episode, increased concentrations of birch pollen were calculated over the European continent and plumes of pollen were transported towards the UK. The arrival of these plumes matched well with observations, showing increased concentrations of pollen at the southern UK sites. The two scenarios show, that the simulated pollen concentrations are affected by radiative feedbacks caused by enhanced air pollution of PM changing the energy balance in the atmosphere through backscattering. The largest effects are obtained in areas with pollen emission and the changes are statistically significant throughout most of the model domain, hence also in regions exposed to long-distance transport.

Conclusion: During episodes of Saharan dust, the atmosphere is in a state that favours long-distance transport of PM and aeroallergens. The high concentration of PM affects the radiative balance in the atmosphere, which in turn significantly affects pollen concentrations increasing co-exposure of pollen and air pollutants.

OA0053 | Microbiota change in mice lung exposed to air pollutants

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Background: Environmental microbes have been associated with both protective and adverse lung effects in chronic lung disease. Although the gut microbiome for human health was relatively well studied, the respiratory microbiome's role in the human response to inhaled pollutants is largely unknown. Our aim was to characterize the bacterial microbiome in lung samples collected in a mouse model exposed to nanoparticles. Our aim was to characterize the bacterial microbiome in lung samples collected in a mouse model exposed to nanoparticles.

Method: Mice were exposed to TiO2 particles (200 $\mu g/m^3$ for 1 hr, and saline control on days 1–5, respectively n = 8) using an ultrasonic nebulizer. We determined the composition of microbial communities present in lung samples by amplifying and sequencing regions of rRNA genes from bacteria (16S). Sequencing of amplified 16S regions was performed on the Roche-454 Life Sciences Titanium pyrosequencing platform. Also, airway inflammation and responsiveness were correlated with lung microbiota.

Results: Relative to controls, TiO2 exposure mice revealed increased hyperresponsiveness and inflammatory cells. Pseudomonas,

Acinetobacter, Brucella, Mesorhizobium, Enhydrobacter, Methylobacterium, Rhizobium, Chryseobacterium, Brevundimonas, Deinococcus, and Micrococcus were differently observed between TiO2 exposure and control miceta. One of them, Deinococcus significantly increased in TiO2 exposure mice compared to control mice. The airway inflammatory cells correlated with Deinococcus.

Conclusion: Nanoparticles changed lung microbial taxa, suggesting that exposure to air pollutants may cause lung inflammation via alterations in the lung microbiota.

OA0054 | Associations between outdoor of PM2.5 with cough and wheeze symptoms in asthmatic children in Korea

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Background: Exposure to traffic-related pollutants poses a serious health threat to residents of major urban around the world. Short-term exposure to air pollution can trigger asthma exacerbation in children, but it is not known which components of air pollution are most important. We monitored their outdoor air pollution and asthma symptoms.

Method: Daily 24-hr personal samples of $PM_{2.5}$, including the elemental carbon fraction, were collected for 40 children with asthma during approximately 1 month each. Asthma Control Questionnaire is a survey tool for the measurement of overall asthma control. We conducted a repeated measure panel study to examine weekly associations between ACQ scores and traffic- and non-traffic air pollutants among asthmatic children.

Results: Of the 40 study participants, 24 were males and 16 were females. The average age was 10 years (range 7-14). The average indoor PM 2.5 was 8.7 μg/m3. The odds ratio for a standard deviation increase in ambient PM2.5 was 1.18 (95% CI 0.89-1.58) for cough and 1.07 (0.73-1.66) for wheeze. Decrements in both PEF and FEV1 were associated with increased personal PM2.5 exposure, with a decrease in PEF of 9.40 L/min (95% CI, −20.43 to 2.08 L/min) and in FEV1 of 0.06 L (95% CI, −0.14 to 0.01 L), both representing an average decline of approximately 3.4%, with the association with FEV1 close to statistical significance.

Conclusion: Cough was more prevalent than wheezing in this inner-city panel of asthmatic children. The study suggesting that the PM2.5 is also most responsible for pollution-related asthma exacerbations among children. Studies that rely on exposure to PM mass may underestimate PM health impacts.

SUNDAY, 2 JUNE 2019
OAS 10
TARGETING SEVERE ASTHMA

OA0055 | Dupilumab reduces oral corticosteroid (OCS) use and severe exacerbations, and improves FEV1 in OCS-dependent, severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps

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Background: Dupilumab (DPL), a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2-mediated inflammation. DPL is approved for the treatment of inadequately controlled, moderate-to-severe atopic dermatitis and, in the USA, for patients (pts) aged ≥ 12 years with moderate-to-severe eosinophilic or oral corticosteroid (OCS)-dependent asthma. In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on DPL 300 mg every 2 weeks vs placebo (PBO) significantly reduced OCS dose, while reducing the severe asthma exacerbation rate and improving pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1), independently of baseline (BL) eosinophil levels, and was generally well tolerated in pts with OCS-dependent, severe asthma. This post hoc analysis evaluated DPL efficacy in pts with OCS-dependent, severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps (CRSwNP/CRSsNP) and without chronic rhinosinusitis or nasal polyps (non-CRS/NP).

Method: Percentage reduction in OCS dose and change in pre-BD FEV_1 from BL to Week 24, annualized severe asthma exacerbation rate during 24 weeks were assessed in CRSwNP/CRSsNP and non-CRS/NP pts.

Results: 72 (DPL n = 31; PBO n = 41)/210 pts reported medical history of CRSwNP/CRSsNP using an e-diary. CRSwNP/CRSsNP pts had higher BL FEV_1 and comparable FeNO levels and eosinophil counts vs non-CRS/NP pts. At Week 24, OCS dose was reduced from BL by least squares mean 75.9% for DPL vs 40.9% for PBO (P = .005) in the CRSwNP/CRSsNP subgroup and by 68.0% for DPL vs 41.1% for PBO (P = .0005) in the non-CRS/NP subgroup. The severe asthma exacerbation rate during 24 weeks vs PBO was reduced by 74.3% (P = .001) and 38.4% (P = .08) in CRSwNP/CRSsNP and non-CRS/NP pts, respectively. At Week 24, DPL vs PBO also improved pre-BD FEV_1 by 0.36L (P = .003) in CRSwNP/CRSsNP pts and by 0.19L (P = .01) in non-CRS/NP pts. Overall, the most frequent TEAE in DPL vs PBO pts was eosinophilia, occurring in 14% vs 1% of pts, respectively (no clinical consequences). Injection-site reactions occurred in 9% of DPL vs 4% of PBO pts.

Conclusion: Dupilumab vs PBO significantly reduced OCS use while reducing severe asthma exacerbations and improving FEV_1 in pts with OCS-dependent, severe asthma with comorbid CRSwNP/CRSsNP and non-CRS/NP, with greater treatment effects in CRSwNP/CRSsNP pts, an asthma subgroup more difficult to control. DPL was generally well tolerated.

OA0056 | Dupilumab improves health-related quality of life in patients with oral corticosteroid-dependent, severe asthma with comorbid chronic rhinosinusitis with and without nasal polyps

Maspero JF[1]; Rabe KF[2]; Castro M[3]; Rice MS[4]; Rowe P[5]; Deniz Y[6]; Amin N[6]; Kamat S[6]; Teper A[5]; Khan A[7]

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Background: Dupilumab (DPL), a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2-mediated inflammation. DPL is approved for the treatment of inadequately controlled, moderate-to-severe atopic dermatitis and, in the USA, for patients (pts) aged ≥ 12 years with moderate-to-severe eosinophilic or oral corticosteroid (OCS)-dependent asthma. In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), in pts with OCS-dependent, severe asthma, add-on DPL 300 mg every 2 weeks vs placebo (PBO) significantly reduced OCS dose, while reducing severe asthma exacerbations and improving pre-bronchodilator forced expiratory volume in 1 second (FEV_1), independently of baseline (BL) eosinophil levels, and was generally well tolerated. This prespecified analysis evaluates the effect of DPL on health-related quality of life (HRQoL) in pts with OCS-dependent, severe asthma who also reported suffering from comorbid chronic rhinosinusitis with and without nasal polyps (CRSwNP/CRSsNP).

Method: Change from BL at Week 24 in HRQoL was assessed by the 22-item Sino Nasal Outcome Test (SNOT-22) in comorbid CRSwNP/CRSsNP pts using a mixed-effect model with repeated measures. Total SNOT-22 scores range from 0 to 110, with lower scores indicating better HRQoL, and a change in total SNOT-22 score of ≥ 8.9 is considered to be clinically meaningful.

Results: 72 (DPL = 31, PBO = 41)/210 pts self-reported a medical history of comorbid CRSwNP/CRSsNP. DPL and PBO groups were comparable in BL disease characteristics, including mean total SNOT-22 scores (43.35 vs 41.15, respectively) and biomarkers of type 2 inflammation. At Week 24, LS mean change from BL in total SNOT-22 score was −10.93 in the DPL group and −2.98 in PBO (LS mean difference vs PBO was −7.95; P = .05). Overall, the most frequent treatment-emergent adverse event in DPL- vs PBO-treated pts was eosinophilia, occurring in 14% vs 1% of pts, respectively (no clinical consequences). Injection-site reactions occurred in 9% of DPL- vs 4% of PBO-treated pts.

Conclusion: Dupilumab vs PBO improved HRQoL, despite a significant reduction in OCS dose, in pts with OCS-dependent, severe asthma with comorbid CRSwNP/CRSsNP, a subgroup of pts that are more difficult to treat. Dupilumab was generally well tolerated.

OA0057 | Efficacy of omalizumab therapy in asthma patients with or without asthma-related and allergic comorbidities

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Background: Comorbidities are common in allergic asthma, and increased IgE levels are associated with both allergic and non-allergic comorbidities. We examined the efficacy of omalizumab in patients with moderate-severe allergic asthma by number of comorbidities.

Method: Patients (12–75 years) with moderate-severe allergic asthma from omalizumab phase III (008/009) / IIIb (EXTRA, INNOVATE) trials were included. Ongoing allergic and non-allergic comorbidities were grouped by frequency (0/1 [008/009]; 0/1/≥2 [EXTRA/INNOVATE]). Omalizumab efficacy vs placebo was examined using the relative rate reduction (RRR) in protocol-defined annualized asthma exacerbations by treatment duration (EXTRA/INNOVATE) and between-group differences in change from baseline in FEV_1 over study weeks were estimated (008/009, EXTRA, INNOVATE). Overall safety results are available in Hanania et al. Ann Int Med 2011; Humbert et al. Allergy 2005; Busse et al. JACI 2001; Solèr et al. ERJ 2001.

Results: The rate of asthma exacerbations was reduced with omalizumab relative to placebo. No consistent pattern in RRR (%[95%CI]) by number of comorbidities (0, 1, and ≥ 2 comorbidities in EXTRA or INNOVATE) was observed (Table) and 95% CIs substantially overlapped. FEV_1 improvements were observed throughout the study with omalizumab vs placebo, irrespective of the number of comorbidities, with no consistent differences and highly overlapping 95% CIs observed between 0, ≥1 comorbidities for 008/009 or 0, 1, ≥2 comorbidities across EXTRA, INNOVATE (Table 1).

Conclusion: Reductions in annualized exacerbations and improvements in FEV_1 were observed for omalizumab treatment vs placebo in patients with moderate-severe allergic asthma. No consistent differences in response were observed in patients with 0, 1, or ≥ 2 comorbidities.

OA0058 | Oral corticosteroid-sparing effects of Anti-IL5 and Anti-IL5 receptor treatments: A real-life study

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Background: Anti-IL5 treatments (mepolizumab, reslizumab) and anti-IL5 receptor treatment (benralizumab) are novel treatments for severe eosinophilic asthma. Studies have shown oral corticosteroid (OCS) sparing effects of mepolizumab and benralizumab. However, in these studies the tapering of OCS is tightly controlled and the tapering-duration relatively short. With this study, we present real-life data on the OCS sparing effects of anti-IL5 treatments and anti-IL5 receptor treatment after 12 months of treatment.

Method: We performed a retrospective study of severe, eosinophilic asthma patients treated with mepolizumab, reslizumab or benralizumab. Change between the treatments was allowed. Data on OCS and additional immunosuppressive treatment were drawn from patient records before anti-IL5/anti-IL5 receptor treatment and after 12 months of treatment.

Results: 82 patients were treated with anti-IL5 or anti-IL5 receptor treatment for at least 12 months. Before initiating treatment 64

		Exacerbation RRR (% [95% CI])			Improvement in FEV_1 (mL [95% CI])		
		0	1	≥2	0	1	≥2
EXTRA	Wk 12	–	–	–	124 (−4, 252)	107 (11, 203)	117 (29, 205)
	EoS (Wk 48)	13 (−39, 45)	34 (10, 52)	21 (−8, 43)	140 (−21, 301)	79 (−31, 188)	70 (−20, 161)
INNOVATE	Wk 12	–	–	–	45 (−88, 178)	86 (−94, 267)	148 (26, 270)
	EoS (Wk 28)	38 (3, 61)	26 (−24, 56)	−8 (−100, 41)	46 (−90, 181)	159 (−31, 349)	213 (51, 374)
008/009	Wk 12	–	–	–	107 (58, 156)	117 (19, 215)	–
	EoS (Wk 16)	–	–	–	84 (34, 135)	74 (−23, 170)	–

patients (78%) were treated with daily OCS and 16 patients (19.5%) were treated with additional immunosuppressive treatment. After 12 months, the number of patients treated with daily OCS was 41 (50%) and the number of patients treated with additional immunosuppressive treatment was 3 (3.7%). The mean daily OCS dose before anti-IL5/IL5 receptor treatment was 11.1 mg of prednisolone (9.9-12.3), and after 12 months reduced to 4.3 mg of prednisolone (3.0-5.5), with a significant reduction of 6.8 mg prednisolone (6.6-8.1), $P < .0001$.

Conclusion: We showed a marked reduction in the number of patients taking daily OCS and additional immunosuppressive treatment and we showed a significant reduction in the daily OCS dose after 12 months of treatment with anti-IL5/anti-IL5 receptor treatment. These real-life data are in line with studies like Sirius and Zonda. Thereto, these data show us a long-term effect of anti-IL5/anti-IL5 receptor treatment on OCS reduction in a clinical setting, where the decision to reduce the daily OCS is a shared decision between the patient and the physician.

OA0059 | Oral corticosteroid prescription patterns in asthma care in the UK and Germany

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Background: Asthma management aims to control symptoms and reduce exacerbation risk using minimum therapy. Poor asthma control substantially increases exacerbation risk, necessitating add-on oral corticosteroid (OCS) therapy, which is associated with substantial adverse effects. Here we describe demographics and clinical features of asthma patients in the UK and Germany and patterns of their OCS use.

Method: Electronic medical records from The Health Improvement Network (THIN) UK database and the German Disease Analyzer (DA) were used. In Germany, DA's general practice (GP) and pulmonology (Pulm) data were analyzed separately. Included patients were ≥ 12 years old with ≥ 1 asthma diagnosis within the study period (1 July 2011 to 28 February 2018) and available data for ≥ 183 days before and ≥ 90 days after cohort entry. Patients reach their long-term use status when prescribed ≥ 450 mg OCS in a 90-day period during follow-up. Baseline characteristics including asthma severity, exacerbation history, comorbidities, and measures of OCS use during follow-up were described overall and by OCS use status (non-user, OCS user including non–long-term and long-term user).

Results: In total, 459,289 asthma patients were identified in the UK, 108,638 in German GP, and 23,743 in German Pulm. During the study period, 29.1% of the UK study population were OCS users and 6.5% were long-term users. In German GP and Pulm, OCS users and long-term users were 15.4% and 5.8%, and 19.2% and 8.0%, respectively. One-year prevalence of long-term use from cohort entry was 3.0% for UK, 2.9% for German GP, and 4.1% for German Pulm. OCS users, particularly long-term users, were older, had more severe asthma, more exacerbations, and generally more comorbidities than non-users. Long-term users had greater mean annual OCS prescriptions than non–long-term users (UK: 3.2 vs. 0.6, German GP: 1.2 vs. 0.6, German Pulm: 1.1 vs. 0.6), as well as greater mean daily OCS dosage (mg, UK: 2.2 vs. 0.3, German GP: 2.2 vs. 0.4, German Pulm: 1.9 vs. 0.4), longer mean prescription duration (days, UK: 7.1 vs. 6.1, German GP: 41.4 vs. 16.8, German Pulm: 34.3 vs. 10.7), and shorter mean gap between prescriptions (days, UK: 99 vs. 353, German GP: 256 vs. 413, German Pulm: 328 vs. 520).

Conclusion: OCS use, including long-term use, is relatively common in asthma treatment in the UK and Germany, suggesting suboptimal asthma management. OCS therapy should be considered carefully to avoid associated adverse effects.

OA0060 | Dietary acid load: A novel nutritional target on the children's obese-asthma phenotype?

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Background: Dietary acid load consists in the difference between endogenously produced non-volatile acid and absorbed alkali precursors. Adherence to Western diets, high in fats and processed foods, is often associated with higher values of dietary acid load, metabolic acidosis and with higher risk of asthma in school-aged children. On the other hand, lungs play a major role on the systemic pH and acid-base regulation. However, the association between diet-induced acid load and asthma has not been investigated. Therefore, we tested if the acidity of the diet was associated with lung function in school-aged children with asthma

Method: Data on 699 children, aged 7 to 12 years, were analysed. Anthropometric measurements were performed to assess body mass index (BMI). Dietary acid load was calculated using potential renal acid load (PRAL) equations from a 24-hour dietary recall administrated to children. Adjusted PRAL for energy intake was applied with the use of the residual method. Lung function and airway reversibility were assessed with spirometry. Asthma was defined by at least a 12% and over 200 mL increase in (FEV1) after bronchodilation or self-reported medical diagnosis with reported symptoms occurring in the past 12 months.

Results: *The prevalence of asthma was 8.4% and 5.4% had a positive bronchodilation . PRAL was positively associated with FEV1 (R = .535, P = .013) and FEF25-75 (R = .466, P = .033) in overweight children with asthma and inversely associated with FEF27-75 (R = -.151, P = .045) in overweight non-asthmatic children.*

Conclusion: Our findings suggest that dietary acid load has a different impact on the lung function of overweight children depending on their asthma status. These findings provide support to explore a new possible dietary regulated mechanism in the obese-asthma phenotype in school-aged children.

MONDAY, 3 JUNE 2019

OAS 11

SENSITIZATION AND GEOGRAPHICAL DIVERSITY OF AIRBORNE ALLERGENS

OA0061 | High-throughput DNA sequencing defines spatiotemporal shifts in airborne grass pollen communities at species level

Griffith GW[1]; Potter C[1]; De Vere N[1,2]; Hegarty M[1]; Brennan GL[3]; Skjøth CA[4]; Osborne NJ[5,6]; Wheeler BW[5]; Rowney FM[5]; Barber A[7]; Clewlow Y[7]; Mcinnes RN[7]; Hanlon HM[7]; Adams-Groom B[4]; Kurganskiy A[4]; Petch GM[4]; Jones L[8,9]; Ford CR[8]; Armitage C[10]; Creer S[3]

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Background: Grass pollen is a potent outdoor aeroallergen, responsible for allergic rhinitis and asthma exacerbation. Whilst there are known variations in sensitivity to pollen from different grass species, these species cannot be distinguished by established methods for monitoring of airborne pollen concentrations. As such, the modelling of changes in aerial-dispersion of pollen from individual grass species is currently not possible and it is not known whether temporal turnover in species composition of airborne pollen matches terrestrial flowering patterns. The aim of this study was to use DNA metabarcoding of trapped pollen grains to obtain species-level discrimination of grass pollen across a network of UK sampling sites.

Method: We used two complementary DNA barcode marker genes (*rbcL* and ITS2) to identify how the taxonomic composition of grass pollen exposure changes across the summers of 2016/17. This involved establishment of a UK-wide network of Burkard Multivial Cyclone Samplers for daily sampling and development of DNA metabarcoding methods to identify the trapped pollen grains.

Results: We found that UK grass species display discrete, temporally restricted peaks of pollen incidence which vary with latitude and longitude across the UK. Grass pollen comprised the majority (*ca.* 60%) of airborne pollen during the summer months, dominated by *Lolium* and *Holcus* spp. Significant amounts of *Agrostis capillaris*, *Poa trivialis*, *Dactylis glomerata* and *Arrhenatherum elatius* (*ca.* 5% of all grass pollen each) were also detected. Thus the taxonomic composition of airborne grass pollen changes substantially across the grass allergy season and changes in total grass pollen concentration. We also demonstrate that flowering and anthesis (pollen release) events may be useful for predicting the incidence of particular species of grass pollen in the air.

Conclusion: Our results demonstrate how targeted, high-throughput sequencing of eDNA can be used to understand the biodiversity of airborne pollen communities and fill a substantial knowledge gap that has persisted over the past 50 years of aerobiology research. By developing more refined aeroallergen profiling, we anticipate that our findings will facilitate the exploration of links between taxon-specific exposure of harmful grass pollen and disease, with concomitant socio-economic benefits.

OA0062 | Assessing quantitative taxon-specific grass pollen biodiversity in time and space using targeted molecular analysis of aerial environmental DNA

Brennan G[1]; Potter C[2]; Adams-Groom B[3]; Barber A[4]; Clewlow Y[4]; De Vere N[5]; Griffith G[2]; Hanlon HM[4]; Hegarty M[2]; Kurganskiy A[3]; Mc Innes RN[4]; Petch G[3]; Osborne N[6]; Skjøth C[3]; Wheeler B[7]; Creer S[1]

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Background: In Europe, grass pollen is the single most important outdoor aeroallergen; 27% of the population are sensitised to grass pollen leading to extensive negative health outcomes. Of particular importance to human health is allergic asthma, which can lead to hospitalisation and can be fatal. Sensitivity towards grass pollen varies between species, of which there are over 150 in the UK. However, due to few unique morphological features, grass pollen from different species cannot be discriminated easily using traditional observational methods. Currently, there is no way of detecting, modelling or forecasting the aerial-dispersion of taxon-specific pollen from the extensive biodiversity of UK grasses. PollerGENis an interdisciplinary NERC project, in collaboration with the UK Met Office with the aim of advancing the way that pollen dispersion is measured and forecast. Emerging molecular data (targeted sequencing of DNA taxonomy markers, i.e. metabarcoding) have indicated that the species composition of aerial grass pollen communities varies significantly both temporally and spatially across the grass flowering season. Yet, the precise quantitative nature of the data, both from laboratory and field trials, remains unconfirmed.

Method: Here, we used quantitative PCR (qPCR) to analyse aerial environmental DNA (eDNA) from up to 14 sites across the UK during the 2016-2017 grass pollen seasons. Our aim was to quantify phenological and geographical trends exhibited in pollen deposition of key known allergenic grasses, including *Dactylis glomerata*, *Lolium perenne and Phleum pratense*.

Results: The results confirm that the grass flowering season is heterogeneous, showing quantitative differences in taxon composition throughout the summer months. The data demonstrate that seasonal exposure to different types of grass pollen is not static, but features shifting abundances of different species of pollen that can be linked to health outcomes.

Conclusion: The empirical findings will be discussed in addition to providing a broader perspective of the PollerGEN program, that integrates species vegetation mapping, advanced aerobiological modelling, environmental genomic, metabarcoding and qPCR genetic analyses and human epidemiology.

OA0063 | Sensitization to holm oak and plane tree pollen and cross-reactivity patterns with grasses of a university student population in Évora, Portugal

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Background: Plane (*Platanus hybrida*) and holm oak (*Quercus rotundifolia*) trees pollen are among the most prevalent in Alentejo with pollination peaks in the early spring (March and April). Despite the high level of exposure of the population, these pollen types are considered moderately allergenic and both the sensitization and their allergen profiles are yet poorly characterized in this region. In this work, we aimed characterizing the sensitization to plane and holm oak pollen among young adults' population to holm oak and plane tree pollen and evaluate their cross-reactivity pattern with grasses (*Dactylis glomerata*).

Method: Fifty volunteers, students in the University of Evora, aged 18-25 years old, were enrolled in this study, after informed consent and Ethical Committee authorization (ref. 15039). A questionnaire was applied to evaluate the prevalence of pollen allergy symptoms. Serum IgE was quantified by specific ELISA. Sensitization to three pollen types (*Dactylis glomerata; Platanus hybrida; Quercus rotundifolia*) was assessed by EAST (Enzymoallergosorbent Assay). Allergen profiles were analysed by immunoblotting and inhibited immunoblotting was used to assess cross-reactivity.

Results: The results of the questionnaire, associated with the IgE levels, suggested that at least 36% of the individuals enrolled in the study might suffer from allergic symptoms during the pollen season. This population was sensitized to at least one pollen type; sensitization prevalence to grasses was ~45% and to holm oak and plane tree pollen types was ~30%. Several bands were identified by EAST positive sera in the range of 10 to 80 kDa, including bands with MW corresponding to Pla a 1 (<20 kDa), Pla a 2 (40 kDa) and Pla TLP (21 kDa) allergens. Positive EAST sera to holm oak pollen identified several protein bands in the MW range of 15 to 65 kDa. Both holm oak and plane tree pollen have shown significant cross-reactivity with grass pollen.

Conclusion: These results evidenced a considerable prevalence of sensitization to plane and holm oak tree pollen in Alentejo, Portugal. Despite mildly allergenic, considering the high levels of exposure, these pollen types may contribute to induce pollinosis or aggravate allergic symptoms on the early spring in this region. A better understanding of complex patterns of cross-reactivity between pollen types, combined with exposure data, might contribute to a better management of seasonal respiratory allergic diseases.

OA0064 | Molecular sensitisation profile to Dermatophagoides pteronyssinus dust mite in Portugal

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Background: In Portugal, dust mite (DM) allergens, namely those of *Dermatophagoides pteronyssinus* (*Dp*), are the most prevalent ones. Aim: to analyse component-resolved diagnosis (CRD) to *Dp* (*rDer p 1*, *rDer p 2*, *rDer p 10 and rDer p 23*) in patients with respiratory allergy to DM, and possible relationship with clinical severity and geographical areas.

Method: We selected 217 patients in 13 centres in Portugal, 5 from North (n = 65) and 8 from South (n = 152). These patients had allergic rhinitis, with or without asthma, positive SPT to at least one of the DM—*Dp*, *D. farinae* (*Df*), *L.destructor* (*Ld*) or *B.tropicalis*, and had never

	sIgE [Median (Q_1-Q_3)] (kU/L)				
	Dp	rDer p 1	rDer p 2	rDer p 10	rDer p 23
Rhinitis	32.80 (6.80-83.40)	17.20 (5.96-46.15)	20.00 (6.14-56.78)	5.69 (1.38-22.60)	6.65 (2.26-18.40)
Rhinitis + Asthma	38.30 (9.00-100.0)	20.35 (6.90-49.33)	23.50 (9.29-67.20)	7.29 (3.16-25.05)	7.32 (2.56-27.40)
Mild Rhinitis	28.30 (5.54-74.80)	14.20 (5.43-42.20)	17.65 (5.46-42.60)	1.36 (1.13-23.50)	6.14 (2.31-13.40)
Moderate/Severe Rhinitis	36.00 (8.20-99.78)	18.15 (6.55-49.78)	22.70 (6.41-66.90)	5.76 (3.66-22.40)	6.87 (2.26-23.60)
North centres	20.80 (5.35-73.95)	7.06 (0.04-23.30)	11.30* (1.96-32.25)	0.00 (0.00-0.03)	2.53 (0.28-9.16)
South centres	35.35 (7.17-84.18)	8.84 (0.14-39.28)	19.10* (4.71-56.08)	0.01 (0.00-0.03)	4.99 (0.81-13.33)

* $P = .0496$.

undergone immunotherapy with DM. sIgE to *Dp*, *Df* and *Lp*, and CRD to *Der p 1*, *Der p 2*, *Der p 10* and *Der p 23* were determined using ImmunoCAP-Thermo Fisher Scientific. Statistical analysis was performed with Mann Whitney U test (rhinitis vs rhinitis+asthma; mild vs moderate/severe rhinitis; Northern centres vs Southern centres).

Results: 217 patients (mean age 25.85 ± 12.7 years; 51.16% females). For all DM, prevalence (patients with sIgE > 0.35kU/L) was 98.2% for *Dp*, 97.2% for *Df* and 84.8% for *Lp*, while corresponding serodominance (median levels of sIgE—kU/L) was 31.9,17.5 and 8.12. For CRD, prevalence of *Der p 1*, *Der p 2*, *Der p 10* and *Der p 23* was 72.4%, 89.4%, 9.7% and 77%, respectively, while corresponding serodominance was 8.56, 17.7, 0.01 and 3.95. Table 1 shows median serum levels of sIgE according to clinical severity and geographical areas.

Conclusion: We confirmed that *Dp* sensitisation is the most common one in Portugal. The most prevalent CRD is *Der p 2*, followed by *Der p 23*, *Der p 1* and *Der p 10*. The major serodominance belongs to *Der p 2*, followed by *Der p 1*,*Der p 23* and *Der p 10*. Although sIgE levels for these CRD were higher in more symptomatic patients, this trend was not statistically significant. The median level of sIgE to *Der p 2* in the Southern centres was higher and statistically significant when compared with Northern centres, which may be related to the largest sample of this region.

OA0065 | Molecular data of pollen sensitization corresponds with pollen spectrum of Ukraine

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Background: Prick-tests, which were used as a conventional method of allergy diagnostics for several decades, were not able to meet all needs of precise allergy diagnostics. The number of allergens was limited there and availability of molecular diagnostics in Ukraine changed the understanding of the relation of patients' sensitivity and allergen exposure.

Method: The data of 1013 patients living in different regions of Ukraine diagnosed using the Allergy Explorer (ALEX) test was analyzed. A comparison was made between the data of molecular sensitization and pollen and spores count obtained in Central and Eastern regions of Ukraine.

Results: Despite the fact that grass pollen is not prevalent in air spectrum of Ukraine, 39% of tested patients had raised amount of 7 specific IgEs to timothy grass included into the Alex panel. Increased levels of fescue sIgE had 29% tested individuals. 35% of patients were sensitized to allergens of ragweed, which are prevalent in southern and south-eastern regions of Ukraine.

Sensitization to birch allergens was seen in 34% of cases, 21.6% of patients were sensitive to alder pollen and 19% – to hazelnut allergens, available in the Alex panel. *Betula-Alnus* sensitization was observed in 21.8% cases. *Betula* and *Alnus*, contribute the most tree pollen in the air of Northern and Central Ukraine. 23.5% of patients were sensitized to pollen of mugwort, that is present in all regions of the country. 23.3% of the tested individuals were sensitive to *Alternaria* allergens, which levels are high and very high in midsummer and autumn in Ukraine. Such sensitization rate to *Alternaria* was not detected in Ukraine before due to the absence of robust diagnostic methods. 18% of tested individuals were sensitized to Olive family pollen. 17.5% of them—to olive allergens, despite this tree does not grow in Ukraine and just 4.6%—to ash, which is common in our country. 8.5% of the patients reacted to cypress pollen—due to its cross-reactions with pollen of thuja, juniper and yew. The lowest sensitization rates (0-1%) were observed for *Cladosporium*, nettle, which levels are high and very high in the air, and for mulberry, poplar, mercuries, wall pellitory, elm and privet, which pollen is also seen in Ukraine.

Conclusion: The highest sensitization rates were seen for grass, ragweed, birch, wormwood, alder and *Alternaria*. The lowest number of sensitized (0-1%) was recorded for *Cladosporium*, nettle, peppermint, mercuries, mulberry, poplar, wall pellitory, elm and privet.

OA0066 | Evaluating the real exposure of allergics to airborne pollen: Too high, too early, too long or too complex?

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Background: To date, high-risk pollen exposure alerts have been provided only via forecasting models and laborious monitoring methods. The aim of this study was to evaluate the "real pollen exposure" to airborne pollen, using automatic, real-time pollen monitoring devices, as well as conventional ones and comparing against symptoms from dedicated cohorts of allergic individuals. The research question was whether it is possible and to what extent to assess the personalised pollen exposure that accurately reflects in the everyday symptom score of an allergic individual.

Method: Airborne pollen has been monitored in Augsburg, Germany, since 2015, using a novel automatic Bio-Aerosol Analyser (BAA 500, Hund GmbH), along with a conventional 7-day recording Hirst-type volumetric trap. In parallel, ocular, nasal and pulmonary symptoms of birch and grass pollen-allergic human volunteers have been registered daily. We investigated for the "genuine" pollen exposure, comparing symptoms against the 3 pollen datasets, A) from conventional device, B) from automatic device with the original pollen classification, C) from automatic device with the manual pollen classification. To achieve the above, different definitions of pollen season start, peak, end and duration were checked.

Results: Only the automatic pollen sampler (but after manually classifying pollen and improving existing algorithms) was more accurately able to predict the onset of symptoms, even in earlier or isolated incidents in November and December. On average, all three pollen monitoring means yielded comparable pollen season peaks for birch and grass airborne pollen seasons. During the main pollen season, pollen coincided and correlated positively with symptoms scores of allergic subjects, irrespective of type of the measurement device used. However, the Hirst-type pollen sampler by rule underestimated the amount of pollen in the air, at least 2-fold.

Conclusion: The actual pollen exposure of allergic individuals can be defined more efficiently by automatic, real-time pollen information, after pollen manual classification. This monitoring system identifies out-of-the-season, early pollen occurrence, which closely reflects in early-season symptoms, whose onset cannot be warned upon with existing conventional techniques. An urgent switch to operational automatic pollen monitoring techniques needs to be made, towards the implementation of timely, personalised management of allergies in the future.

MONDAY, 3 JUNE 2019

OAS 12

NEW PERSPECTIVES FROM CLINICAL TRIALS IN IMMUNODEFICIENCIES

OA0067 | Association between severe IgA immunodeficiency and allergic and respiratory disorders in children

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Background: Primary immunodeficiency disorders (PIDs) are identified as a heterogeneous group of genetic disorders. The most common primary immunodeficiency in many ethnic populations is selective immunoglobulin A deficiency (sIgAD), which incidence varies from 1:163 to 1:18500. Children with sIgAD are often asymptomatic but they can suffer from allergic diseases, recurrent mucosal infections and autoimmune disorders. Our aim was to investigate the correlation between different clinical manifestation and severe sIgAD and to better understand the association between immunodeficiency and respiratory and allergic disorders in children.

Method: Children with IgAD were recruited in paediatric pulmonology, allergology and immunology clinic of Srebrnjak Children's Hospital. Severe IgAD was defined in 45 children over 4 years old, where serum IgA level was < 7 mg/dL, with normal levels of serum IgG and IgM level. All patients were evaluated by their clinical and laboratory investigation parameters and allergy disorders data (eczema, rhinitis, asthma), and compared to control group of children with normal immunoglobulin levels.

Results: Spirometry test results showed that there was a statistically significant difference in lung function for PEF, MEF50 and FENO between group of patients with severe IgAD and control group, where children with IgAD showed reduced lung function. There was no statistically significant difference for FEV1, although children with severe IgAD showed lower values of FEV1. In addition, children with severe IgAD had higher prevalence of asthma, allergic rhinitis and total number of respiratory infections compared to controls, which was statistically significant.

Conclusion: Children with severe sIgAD are at increased risk for recurrent respiratory infections, reduced lung function and developing of allergic diseases. This is the reason why specific immunologic evaluation and detailed analysis of connection between sIgAD and other disorders is needed. More specific and detailed screening should lead to a better outcome and better quality of life for children suffering from sIgAD.

OA0068 | Low dose azithromycin prophylaxis reduces respiratory exacerbations in primary antibody deficiencies: A multicenter, double-blind, placebo-controlled randomized clinical trial

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Background: Lacking protective antibodies, patients with Primary Antibody Deficiencies (PAD) suffer from frequent respiratory. Despite appropriate therapy, patients might develop chronic infection-related pulmonary diseases, including bronchiectasis, Chronic Obstructive Pulmonary Disease (COPD), and asthma. Macrolides prophylaxis has been proven to be effective to successfully manage chronic lung diseases as cystic fibrosis, bronchiectasis, COPD. Based on these observations we conducted a trial to evaluate the efficacy and safety of orally low-dose azithromycin prophylaxis when added to the usual care in PAD patients.

Method: A 3-year, phase II, prospective, multicenter, randomized, double-blind, placebo-controlled trial recruited PAD patients aged 18-74 years with chronic infection-related pulmonary disease. Patients received azithromycin 250 mg or placebo once daily three-times a week for 24 months. The primary endpoint was the decrease of annual episodes of respiratory exacerbations. Secondary endpoints included: time to the first exacerbation, additional doses of antibiotics, number of hospitalizations, Health Related Quality of Life measures, and safety.

Results: Forty-four patients received azithromycin (n = 44) and 45 patients received placebo. The mean number of exacerbations was 3·6 per patient-year (95%CI 2·5-4·7) in the azithromycin arm, and 5·2 (95%CI 4·1-6·4) in the placebo arm (P = 0·02). In the azithromycin group, the HR for having an acute exacerbation was 0·5 (95%CI 0.3-0·9, P = .03) and the HR for hospitalization was 0.5 (95%CI 0.2-1·1) (P = .04). The rate of additional antibiotic treatment per patient-year was 2·3 (95%CI 2·1-3·4) in the intervention and 3·6 (95%CI 2·9-4·3) in placebo groups (P = 0·004). Improvement in HRQofL was observed in the intervention group. No serious AEs drug-related or drug-related causes of discontinuation were reported in the intervention group. H. influenzae and S. pneumoniae were the prevalent isolates

and they were non-susceptible to macrolides in 25% of patients of both arms.

Conclusion: In PAD with respiratory exacerbation, azithromycin prophylaxis led to reduction of exacerbation episodes, of additional courses of antibiotics, and of risk of hospitalization. The low azithromycin dosage increased patient adherence and minimize adverse effects. Given the deleterious effects of respiratory diseases, especially on the risk of death, quality of life, and cost of care, adding azithromycin to PAD treatment should be considered as a valuable option.

OA0069 | BCG vaccine-associated complications and clinical course following allogeneic bone marrow transplantation in patients with primary immunodeficiency diseases

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Background: Bacillus Calmette-Guerin (BCG) is a live attenuated vaccine, that may pose a risk to patients with primary immunodeficiency diseases (PID). We aim to highlight the risk of BCG-related complications in PID patients.

Method: This is a retrospective analysis of PID patients diagnosed at Hadassah-Hebrew University Medical Center, between 2007-2018, and developed BCG-associated complications. We gathered data regarding genetic susceptibility, clinical characteristics, course and outcome.

Results: Eighteen patients with BCG related complications were identified; nine children with mendelian susceptibility to mycobacterial disease (MSMD) and nine PID patients that underwent hematopoietic stem cell transplantation (HSCT). The second group included 8 severe combined immune deficiency (SCID) patients and one with VPS-45 mutation. Mean ages at presentation of MSMD and SCID patients were 4.1 (range: 0.2-17) years and 7.8 (4-12) months, respectively. IL12RB1 was the most common mutation among MSMD patients. One MSMD patient died due to liver and brain abscesses and two SCID patients due to disseminated BCG infection following HSCT engraftment. Pretransplant BCG vaccine-related complications were associated with poor prognosis.

Conclusion: Caution is required in PID patients before administering BCG vaccination. Detailed background including family history of PID and consanguinity is crucial and could be life-saving especially in areas where the high rate of consanguinity still contributing to high rate of autosomal recessive PIDs with fatal outcome and devastating complications.

OA0070 | Impact of the route of immunoglobulin administration on health-related quality of life in patients with CVID: A prospective multicenter study

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Background: Since 1980s, immunoglobulin replacement therapy (IgRT) has led to a profound change in morbidity and mortality of patients with Common Variable Immune Deficiencies (CVID), the most common clinically relevant primary immunodeficiency. Since CVID patients require therapy for life, the acceptability of the different schedules and setting for Ig administration are important instruments to achieve adherence to treatment and to preserve the health-related quality of life (HRQoL) of patients. In this multicentre study, we aimed to assess the HRQoL in CVID adults receiving different schedules of IgRT by intravenous (IVIG), subcutaneous (SCIG) and facilitated (fSCIG) preparations. For these patients, IgRT schedule was chosen after a period focused on identifying the most suitable individual option and possibly minimizing the burden of treatment.

Method: 327 participants were enrolled in a prospective, observational, 18-months study. Participants received IgRT for at least two years. The first 6-months were devoted to the educational process during which the choices related to IgRT were regularly re-assessed, and the shift to alternative regimen was permitted. During the following 12-months, clinical data were prospectively collected and only patients who did not further modify their IgRT schedule were included in the analysis of HRQoL measured by CVID_QoL, a specific instrument, and by GHQ-12, a tool to assess minor psychiatric nonpsychotic disorders.

Results: 304 patients were included in the analysis. CVID_QoL global score, and its dimensions (Emotional Functioning, Relational Functioning, Gastrointestinal symptoms) were similar in IVIG, SCIG and fSCIG recipients. Patients under fSCIG less likely had a GHQ-positive status in comparison to patients receiving IVIG (P = .01; OR 3.2, 95%CI 1.3-7.7), and SCIG (P = .01; OR 3.0, 95%CI 1.1 to 8.4). Univariate analysis showed that patients receiving IgRT by different routes of administration reported similar capacity to make long-term plans, discomfort due to therapy, and concern to run out of medications. Multivariate analysis revealed the GHQ-12 status, but not the IgRT mode of administration, as the major factor impacting on treatment-related QoL items, and a significant impact of age on discomfort related to IgRT.

Conclusion: IgRT schedules do not impact the HRQoL in CVID if the treatment is established after an extensive educational period focused on individualizing the best therapeutic regimen.

OA0071 | Autoimmunity and lymphoproliferation: Different or converging phenotypes in common variable immunodeficiencies?

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Background: Common Variable Immunodeficiencies (CVID) represent the most frequent symptomatic primary immunodeficiency and are defined by hypogammaglobulinemia due to defects in peripheral B-cell differentiation and disturbances in T-cell subsets. The immunologic and clinical diversity of CVIDs hampers phenotype categorization, and the discovery of underlying disease-causing mechanisms and of relevant clinical/laboratorial prognostic factors. This study aims to evaluate the stability of the clinical phenotype of CVID patients and to address possible associations between clinical manifestations and B and T cell disturbances.

Method: We reviewed the medical records and immunological data of 60 adult patients, (mean age 45 ± 13 years; mean length of follow-up 8.5 years, up to 24). We further focused our analysis in a subgroup of 29 patients from whom we have detailed clinical evaluations performed 7 years before. In addition to peripheral B-cell populations, we extended flow-cytometric analysis to quantify the loss of naïve CD4 T-cells and degree of T-cell activation. We compared these parameters in CVID groups split according to the presence of a given clinical manifestation and with an age-matched healthy group, and evaluated the stability of the clinical phenotype, through the analysis of the largest adult cohort under follow-up in a portuguese Centre.

Results: The initial manifestations of CVIDs were recurrent respiratory infections in 63% of the 60 patients. Nevertheless, there was a high prevalence of autoimmunity, lymphoid proliferation and malignancy; which expanded throughout 7 years follow-up in the subgroup of 29 patients with longitudinal data available. This expansion occurred despite adequate IgG replacement, either endovenous or subcutaneous. Autoimmune cytopenias, splenomegaly, adenopathies and lymphoid proliferation were associated with significantly higher levels of T-cell activation markers, naïve CD4 T-cell loss and expansion of $CD21^{low}CD38^{low}$ B-cells. The majority of the infectious and non-infectious clinical manifestations did overlap, and an infection-only profile was confined to only 3 patients.

Conclusion: Our data support that the clinical phenotype categorization of CVIDs is dynamic, evolving throughout follow-up with progressive overlap of non-infectious manifestations. Additional therapies are required to contain the emergence of non-infectious complications that are the main determinants of morbidity in CVID patients.

MONDAY, 3 JUNE 2019
OAS 13
MOLECULAR FEATURES OF ALLERGENS

OA0072 | The crystal structure of the major olive pollen allergen Ole E 1 elucidates the dimeric nature of the allergen and explains its high allergenicity

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Background: In the research field of molecular allergology, structural investigations of important allergens are crucial for the development of hypoallergenic derivatives and the design of efficient vaccines. An important allergen source in the Mediterranean area is the olive tree pollen. The major allergen in these pollen is Ole e 1 that is recognized by 90% of atopic individuals with olive tree pollinosis. So far, only one homologous structure was solved and therefore only little structural information is available for the Ole e 1-like family of allergens. This work elucidates a new structural understanding of this protein family.

Method: recombinant Ole e 1 was produced natively folded in E. coli, characterized with biophysical methods and compared to natural Ole e 1. The three-dimensional structure was solved using X-ray crystallography. Peptide-based IgE-binding and inhibition assays were performed to map the dominant IgE-epitope regions of Ole e 1.

Results: We here present the 3D crystal structure of the major olive tree pollen allergen Ole e 1, the prototypic member of the Ole e 1-like family. The structure exhibits a 6-stranded β-barrel in the core, resembling the fold of Pla l 1, which is the only other known structure of this allergen family (PDB-Code: 4Z8W). Additionally, the C-terminus, which is missing in the homologous structure, forms an α-helix that serves as the interface for a homodimer formation. Stable dimer formation was also proven in solution. Immunological characterization revealed the high allergenicity of the allergen and enabled the determination of IgE-epitope regions.

Conclusion: The 3D structure of Ole e 1, the prototypic member of the Ole e 1-like family shows that these allergens most likely act as dimers in solution and that the C-terminal extension is crucial for dimer formation. In combination with immunological data are able to map putative IgE-epitopes of Ole e 1 and to explain its allergenic potential. These findings will enable new strategies for vaccine development.

OA0073 | Pru P 7 is a major peach allergen associated with cypress pollen sensitization and increased risk of severe reactions

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Background: Peach is a common elicitor of immediate food allergic reactions, occurring both as pollen-food syndromes and as primary food allergies. Pru p 7 has gained attention as a potential peach allergy (PA) severity marker. We sought to investigate the distribution

and clinical characteristics of Pru p 7 sensitisation among subjects with suspected PA in different regions of France.

Method: A total of 316 subjects with suspected PA were included. Diagnostic workup performed according to current guidelines established PA in 198 of these and peach tolerance (PT) in 118. IgE measurements and competition experiments were performed using the ImmunoCAP assay platform.

Results: A gradient of Pru p 7 sensitisation from north to south was observed (Lyon 29%, French Riviera 60%, $P = .003$). Pru p 7 sensitisation was more frequent in PA (62%) than in PT (41%) patients, $P = .0002$, and in PA patients who experienced systemic reactions (78%) vs grade 2 (64%) or grade 1 (39%) reactions, $P < .0001$. Apparent monosensitisation to Pru p 7, i.e. without detectable IgE to Pru p 1, Pru p 3, Pru p 4, was more frequent in PA than in PT patients (54% *vs* 17%, $P < .0001$).

The concentrations of IgE to Pru p 7 were higher in PA than PT patients sensitised to this allergen (median 3.4 *vs* 0.3 kU_A/L, $P < .0001$). Likewise, the severity of peach-induced reactions was significantly associated with the concentration of IgE to Pru p 7. Cofactor involvement (22/171 *vs* 7/145, $P = .01$) but not eyelid edema (15/171 *vs* 5/145, $P = .06$) was more frequent in Pru p 7-sensitised patients. All but one among the 171 Pru p 7 sensitised subjects were also sensitised to cypress pollen (CP). Preincubation with different concentrations of CP extract caused a gradually increasing and ultimately almost complete (98-99%) inhibition of IgE binding to Pru p 7. In contrast, preincubation with Pru p 7 only partly (67-72%) prevented IgE binding to immobilised CP extract.

Conclusion: Pru p 7 sensitisation is common in patients allergic to peach, often in the absence of sensitisation to other peach allergens. Sensitisation to Pru p 7 is associated with CP sensitisation and appears to be driven by CP exposure, rather than reflecting a primary food sensitisation. Because CP is present in continental as well as Mediterranean environments, and given the worldwide distribution of related *Cupressaceae* species, Pru p 7 and homologous food proteins may be important culprits in severe allergic reactions to peach and other plant foods in many regions of the world.

OA0074 | Assessment of Tri a 14 sensitization in the routine allergological study: Analysis of currently available diagnostic tools efficiency

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Background: LTP (Lipid Transfer Protein) allergy is the main cause of plant food allergy in the adult population of the Mediterranean area. Tri a 14 (wheat LTP) has been described as a major allergen associated with wheat allergy in our area and relevant in wheat-induced anaphylaxis, also associated to cofactors and with a clinical phenotype equivalent to the well-known Wheat-Dependent Exercise-Induced Anaphylaxis linked to w5-gliadin sensitization.

Objective: To evaluate and compare the diagnostic efficiency of wheat Skin Prick Test (SPT), wheat-specific IgE (sIgE) and Tri a 14 by ImmunoCAP ISAC®, to detect LTP sensitization in patients found sensitized to Tri a 14 by ImmunoCAP®.

Method: 120 adult patients sensitized to Tri a 14 by ImmunoCAP® (cut-off ≥ 0.1 kU_A/L) were included. Data on SPT with commercial extract of wheat (LETI, Madrid, Spain), total IgE, specific IgE to wheat whole extract (f4) and Tri a 14 (f433) (ImmunoCAP®) and microarray ImmunoCAP ISAC® (cut-off 0.3 ISU) (Thermo Fisher Scientific, Sweden) were collected and evaluated.

Results: The 120 patients analyzed for the study had a median sIgE to Tri a 14 of 0.92 kU/L [interquartile range (IQR) 0.35-2.67]. Of them, 79 had been skin-prick tested with wheat which was negative in 57% (45/79) of cases. For wheat serum sIgE (median 0.66 kU/L [IQR 0.2-1.4]), data were available for 107 patients, being positive in 86% (92/107) when a cut-off ≥ 0.1 kU_A/L was considered and 65% (69/107) of cases with the cut-off ≥ 0.35 kU_A/L. Tri a 14 sIgE levels were two times higher than wheat sIgE in most patients (78%) (median 2.2 kU/L [IQR 0.8-4.3]). Regarding microarray, data were available for 69 patients, being Tri a 14 negative in 80% (55/69) (median 0.5 ISU [IQR 0.15-0.8]).

Conclusion: SPT with wheat and Tri a 14 sIgE using ImmunoCAP ISAC® failed to detect wheat and Tri a 14 sensitization in most patients. Tri a 14 is underrepresented in wheat extracts used for SPT and sIgE determination and using the cut-off value ≥ 0.35 kU_A/L, the 35% of patients sensitized to Tri a 14 go undetected. It seems that the determination of Tri a 14 sIgE by ImmunoCAP® with the cut-off ≥ 0.1 kU_A/L is the most efficient tool.

OA0075 | N-terminal vicilin domains are major allergens in walnut

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Background: Vicilins are storage proteins of the cupin family found in the seeds of many plants. They are homotrimers with molecular weights of 150–190 kDa and have been reported as allergens in several species. Vicilins are synthesized as pre-proteins with varying numbers of cysteine-rich repeats located N-terminally of the cupin domain. The N-terminal region, often referred to as vicilin_N, is processed into peptides of 50-60 amino acids containing a CXXXC-$X_{(10-12)}$-CXXXC motif. Two vicilin allergens, Jug r 2 and Jug r 6, have been described in walnut, the cupin domains of which are 48% identical. The vicilin_N peptides have in other species been shown to have anti-microbial and anti-fungal properties. The aim of this study was to investigate the allergenic significance of the vicilin_N peptides in walnut.

Method: Vicilins and vicilin_N peptides were isolated from walnut extract. Amino acid sequences were determined by MS/MS using an Orbitrap Fusion instrument and compared with relevant walnut genome database entries. Jug r 6, mature Jug r 2 (cupin domain only)

and the entire Jug r 2 N-terminal domain were expressed as hexahistidine tagged proteins in E. coli or P. pastoris and purified by immobilized metal ion affinity and ion exchange chromatography. IgE antibody measurements were performed by ImmunoCAP in sera of 198 walnut sensitized adult subjects.

Results: Jug r 6 appeared to be the most abundant vicilin in walnut extract whereas only minute amounts of the processed Jug r 2 cupin domain was found. A combination of MS/MS and bioinformatic analysis revealed that Jug r 2 is synthesized with six vicilin_N repeats while Jug r 6 only has one. Following natural processing, vicilin_N peptides accumulate as apparently stable protein fragments. Of the 198 tested sera, 28% showed IgE antibody binding to rJug r 6, 36% to the Jug r 2 cupin domain and 50% to the Jug r 2 N-terminal domain. In most cases, the Jug r 2 N-terminal domain showed several fold higher IgE binding than Jug r 2 cupin and Jug r 6. Only five subjects had IgE antibodies to Jug r 6 but not to the Jug r 2 N-terminal domain. These sera either tested negative to Jug r 2 cupin or had lower titers compared to Jug r 6.

Conclusion: Our results suggest that the Jug r 2 N-terminal domain is a major walnut allergen and an important addition to the panel of allergens useful in the diagnosis of allergy to walnut. Jug r 6 is a minor allergen, but may be relevant in a minority of walnut allergic patients.

OA0076 | Intermolecular association of peanut allergens and the impact of thermal processing

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Background: Much is known regarding the sequences and the level of expression of peanut allergens. However, proteins in high-density, low water conditions, such as those in peanut seed, may be subject to intermolecular associations that are difficult to study. Such associations may have implications for food allergen sensitization and elicitation, as well as behavior during food processing and digestion in the GI tract. To study associations between peanut proteins, we used size-exclusion chromatography (SEC) with offline mass spectrometry (MS) to detect and quantify peptides in individual size fractions. This technique was applied to raw and thermally processed peanuts in the presence or absence of chaotropic reagents to solubilize and analyze heavily aggregated material which is absent from most studies.

Method: Raw peanuts, commercially roasted and lab-roasted peanuts (var. Runner) were defatted and extracted in TBS or GuHCl buffer, clarified, and applied to a Superdex 200 SEC column. Fractions were reduced, alkylated, and digested prior to analysis by LC-MS/MS using an untargeted data-dependent acquisition method. Label-free quantitation of allergenic peanut proteins was performed using a database of peanut allergen proteins derived from the peanut genome, or from the entire UniProt peanut database.

Results: The elution profiles of the prolamins Ara h 2, 6 and 7 indicated that they were present as monomers. Ara h 1 and 3 were primarily trimmers or hexamers. The *N*-terminal region of Ara h 1 is cleaved and present as a distinct, monomeric molecular entity. Association of Ara h 2 and 6 with cupins (eluting at > 150 kDa) was observed, but interestingly, this phenomenon was limited to only a subset of Ara h 2 peptides. Roasting severely reduced detection of Ara h 1, and appeared to cause an increase in the apparent mW of Ara h 2 and 6.

Conclusion: SEC with offline MS offers a promising, data-rich method for examining the oligomeric state of many (>100) proteins within one experiment. Peanut seeds contain major allergenic proteins which interact with one another. The association of Ara h 2 and cupin proteins was unexpected. Cross-reactivity of IgE recognizing Ara h 2 with 3 has been observed, and the association may offer an explanation. The *N*-terminal region of Ara h 1 is present as an independent molecule, not associated with the mature form of Ara h 1. The allergenicity of this product of Ara h 1 is unknown.

OA0077 | CCD interference in the diagnosis of allergy to shellfish and parasitic helminths

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Background: Cross-reactive carbohydrate determinants (CCDs) interfering with proper in vitro allergy diagnosis are known from plants and some invertebrates including insects, mollusks and certain parasitic worms. While the role of CCDs has been thoroughly studied in pollens, plant food, latex and insect venoms, little is known about their importance in the diagnosis of shellfish and parasite allergy.

Method: 10 CCD-positive control sera (bromelain 6.43-100 kU/L) as well as 10 CCD-positive sera from patients with a history of shrimp allergy (shrimp 0.41-10.4 kU/l, bromelain 0.72-29.9 kU/L) were tested on extracts from shrimp, oyster, mussel, squid (Loligo sp.) and the parasitic nematodes Ascaris and Anisakis using Phadia ImmunoCAP. Sera were tested on the same allergens also after CCD inhibition with a commercial CCD blocker (MUXF3-HSA, 20 µg/mL).

Results: All CCD control sera were strongly positive to oyster (5.20-87.4 kU/L, 73 ± 13% of bromelain reactivity) and squid (2.80-34.0 kU/L, 54 ± 26%) and to a lesser degree also to mussel (0.48-23.4 kU/L, 20 ± 14%) and shrimp (0.66-9.44 kU/L, 13 ± 6%). IgE reactivity strongly correlated with IgE binding to bromelain (r = 0.82-0.99) and between the different shellfish species (r = 0.60-0.91) and could be inhibited > 95% by the CCD inhibitor. CCD-positive sera also moderately bound to Ascaris (10 ± 5% of bromelain) and Anisakis (6 ± 2%). Nearly all of the 10 CCD-positive shrimp-allergic patients were positive also to oyster (0.25-41.2 kU/L), squid (0.43-23.8 kU/L) and mussel (0.18-20.9 kU/L). CCD inhibition revealed that IgE-binding to shrimp was due to protein epitopes in 6/10 patients and due to CCDs in 4/10. The reactivity with mollusks was mostly due to CCDs alone (oyster 8/10, mussel 8/10, squid 9/10).

Conclusion: Extracts from oyster, mussel and squid contain high amounts of CCDs causing false-positive test results already in sera with low levels of CCD-specific IgE. The occurrence of CCDs also in crustaceans (shrimp) was unexpected and thus far unknown. Clinically irrelevant cross-reactivity through CCDs has to be borne in mind when exploring cross-sensitization to different shellfish species in patients with a history of shellfish-allergy.

OA0078 | Establishment of an allergic lung inflammation mouse model for pre-clinical testing of novel anti-human IgE drug candidates

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Background: Immunoglobulin E (IgE) plays a central role in the pathophysiology of allergic asthma. It binds with high-affinity to its primary receptor FcεRI on airway mast cells. Upon inhalation of the cognate allergen, IgE-sensitized mast cells degranulate and release soluble mediators causing allergic symptoms. The therapeutic anti-IgE antibody omalizumab prevents the binding of free serum IgE to FcεRI and has proven efficient for the treatment of severe persistent allergic asthma. We have recently described a novel class of disruptive anti-IgE inhibitors, which not only suppresses the binding of IgE to FcεRI but also actively removes FcεRI-bound IgE from allergic effector cells. Here, we describe the establishment of an allergic lung inflammation model using double transgenic mice expressing the human immunoglobulin epsilon heavy chain (huIgε) and the human FcεRI alpha-chain (huFcεRIα), which will allow and facilitate future pre-clinical testing of such novel anti-human IgE drug candidates in vivo.

Method: Double transgenic huIgε/huFcεRIα$^{+/+}$mice were epicutaneously sensitized with ovalbumin in combination with the vitamin D analogue MC903 prior to intranasal antigen challenge. After four consecutive antigen challenges, cellular and molecular parameters of lung inflammation were analyzed. Single cell suspensions from blood and lung tissue were measured by flow cytometry. Blood plasma and lung tissue were analyzed for total and allergen-specific IgE, mast cell-specific protease 1 (MCPT-1) and basophil-specific MCPT-8. Gene expression of *Muc5ac*, which encodes a protein predominantly produced and secreted by goblet cells in the airway epithelium, was analyzed by quantitative PCR. Besides, histological section of skin and lung tissue were stained by immunohistochemistry.

Results: Increased total and allergen-specific IgE was detected in sensitized compared to control treated mice. The number of basophils, eosinophils and mast cells in the lung were markedly augmented after sensitization. While basophil specific-*Mcpt8* expression in the lung was upregulated during sensitization, increased expression of mast cell-specific-*Mcpt1* and epithelial *Muc5ac* were observed mainly after intranasal challenge.

Conclusion: With the establishment of this adjuvant free allergic lung inflammation model in huIgε/huFcεRIα+/+ double transgenic mice, we provide an interesting possibility to facilitate pre-clinical in vivo testing of novel anti-human IgE drug candidates, such as disruptive IgE inhibitors.

OA0079 | MARCKS family proteins are altered in naturally occurring model of asthma in horses

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Background: Asthma is a significant health concern that affects people of all ages worldwide. Equine asthma syndrome (EAS) demonstrates many of the pathophysiological characteristics of nonatopic human asthma, which has led EAS to be used as naturally occurring model. In horses with EAS, neutrophils in the airways contribute to the inflammation and tissue damage, making them a potential target for new therapies. Previous work from our lab determined that MARCKS (Myristoylated Alanine Rich C Kinase Substrate) protein is an essential regulator of multiple neutrophil functions. In the current study, we hypothesized that MARCKS family proteins would be increased in BAL cells from horses with EAS, and that inhibition of MARCKS in LPS-stimulated BAL cells (*ex vivo*), with an inhibitor peptide known as MANS, would diminish production of inflammatory mediators. Our goal is to obtain proof of principle data to support MARCKS inhibition as a viable therapeutic approach for EAS.

Method: Lysates were prepared from BAL cells isolated from horses with no (n = 4), mild/moderate (n = 10) and severe (n = 5) EAS. Relative MARCKS protein and MARCKS-like protein 1 (MARCKSL1) expressions were determined using BCA (to quantify total protein) and an equine-specific MARCKS and MARCKSL1 ELISA (MyBioSource). Cultured BAL cells were pretreated with a MARCKS inhibitor peptide (MANS), control peptide (RNS) or vehicle control and stimulated with LPS for 18 hours or left unstimulated. An equine-specific TNFα ELISA (Genorise) was used to quantify TNFα in supernatants (n = 2) and cell lysate (n = 1). Data were analyzed by One-way ANOVA ($P < 0.05$). Preliminary data have not been analyzed.

Results: We determined that normalized MARCKS and MARCKSL1 protein expressions are significantly increased in BAL cell lysates from horses with mild/moderate or severe EAS, compared to horses with normal BAL cytology. Preliminary findings also suggest that MANS treatment of LPS-stimulated equine BAL cells *ex vivo* attenuates levels of TNFα in cell lysates and culture supernatants.

Conclusion: These findings point to a possible role for MARCKS family protein in the pathophysiology of EAS and support MARCKS family protein inhibition as a potential therapeutic strategy.

OA0080 | Metabolic characterization of epithelial barrier damage caused by Der P 1

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Background: Airway epithelium (AE) is one of the largest body surfaces exposed to the environment. In the past years, evidence has arised indicating an association between epithelial airway dysfunctionality and allergic asthma. One of the most common comorbidities of asthma is house dust mite (HDM) allergy. It has been shown that Der p 1, the main allergen of HDM, can disrupt the epithelial airway barrier due to its cysteine-protease action against cellular apical junction complexes. In the last decade, metabolomics has been successfully employed as a new approach to describe metabolic changes in biological systems. Our aim is to use metabolomics as a new approach to analyze the immune response of the airway epithelium to Der p 1 in comparison to a non-proteolytic allergen, Ole e 1 from olive pollen.

Method: Bronchial epithelial Calu-3 cells were grown in an air-liquid interphase to mimic AE spatial distribution. Calu-3 cells were apically exposed to 100 µL of Der p 1 or Ole e 1 allergens for 24 hours, and PBS-exposed cells were used as control. The cell media from the apical and basolateral compartments of the culture system were analyzed by a multiplatform approach consisting of liquid chromatography and capillary electrophoresis both coupled to mass spectrometry (LC-MS and CE-MS, respectively).

Results: Metabolic profiles were obtained using LC-MS and CE-MS; these encompassed 789 and 985 chemical signals for apical and basolateral cell media, respectively. After statistical analysis, we observed that metabolic signaling was performed mainly in the apical side rather than in the basolateral one. Moreover, a specific metabolic pattern was found for Der p 1-exposed cells compared to Ole e 1-exposed and control cells. Significant changes suggested an alteration in the route of nitric oxide (NO) synthesis, tryptophan and folic acid pathways and purine ribonucleotides synthesis, all of which are associated with inflammation and Th2 response.

Conclusion: Epithelial cells try to adapt and respond to the harmful stimulus of Der p 1, a response which is not observed with other allergens such as Ole e 1. This new approach using metabolomics can be useful in the research of allergic HDM asthma.

OA0081 | Cadherin-related family member 3 upregulates the effector functions of eosinophils

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Background: A coding single nucleotide polymorphism in cadherin-related family member 3 (CDHR3) is related with severe exacerbation of childhood asthma. Furthermore, CDHR3 is a receptor for rhinovirus (RV) C, which is closely linked to wheezing illnesses. A genetic variant increases CDHR3 (receptor) expression, RV-C binding and progeny yields, and the severity of illnesses, suggesting that CDHR3 may contribute to the pathogenesis of asthma exacerbation. However, the effect of CDHR3 on immune cells including eosinophils has not been examined. In this study, we examined whether CDHR3 could modify eosinophil functions such as adhesion, superoxide anion (O_2^-) generation, and degranulation.

Method: Eosinophils were obtained from healthy volunteers, and their adhesion to CDHR3 was measured using eosinophil peroxidase assays. Eosinophil O_2^- generation was measured as superoxide dismutase-inhibitable reduction of cytochrome C. Eosinophil-derived neurotoxin (EDN) concentrations in cell media were measured as a marker of degranulation.

Results: CDHR3 induced eosinophil adhesion, which was enhanced by IL-5. CDHR3 also induced eosinophil O_2^- generation and EDN release. Anti-αM or anti-β2 integrin antibody suppressed the eosinophil adhesion, O_2^- generation, and EDN release induced by CDHR3.

Conclusion: These findings suggest that CDHR3 upregulates eosinophil adhesion, O_2^- generation and degranulation. These effects may contribute to the development of eosinophilic inflammation during asthma exacerbations.

OA0082 | EQTL and gene expression analyses using whole genome sequence and RNAseq identify three independent signals in Chr17q region associated with asthma and asthma exacerbations

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Background: SNPs in chr17q region have been consistently associated with asthma, however, the functional SNPs or genes are not obvious due to strong linkage disequilibrium (LD) structure in this region. In this study, we comprehensively investigate all the SNPs and mRNA expression in this region to dissect functional genes for asthma in the SARP1,2,3 cohort.

Method: eQTL analysis of 3,074 SNPs (862 common SNPs) in 16 genes (PPP1R1B to CSF3; chr17:39,626,924-40,017,813) was performed in 114 SARP3 subjects with whole genome sequence (sequenced through the NHLBI-sponsored Trans-Omics for Precision

Medicine (TOPMed) Program) and RNAseq data in cells from human bronchial epithelial biopsy (BEC), and replicated in 120 and 108 SARP1,2 subjects with genome-wide association study (GWAS) and microarray expression data from BEC and from bronchial alveolar lavage (BAL), respectively. Correlation analysis of gene expression and asthma phenotypes were performed in 156 SARP3 subjects with RNAseq in BEC, and replicated in 155 and 154 SARP1,2 subjects with microarray expression data, respectively.

Results: 273 effective SNPs were extracted from 862 common SNPs using LD-based pruning (r^2>0.8). eQTL analyses identified 26 of 273 effective SNPs significantly associated (P < 1.8E-4) with RNAseq expression levels of PGAP3, GSDMB, or GSDMA in BEC of SARP3, and confirmed in eQTL analyses in BEC or BAL of SARP1,2. Conditional association analysis indicated that 2 independent SNPs (rs2517954 in PGAP3 and rs114211283 in IKZF3), 2 independent SNPS (rs11657449 in ZPBP2-GSDMB and rs3794712 in PPP1R1B), and 1 SNP (rs3859193 in GSDMA) were eQTL SNPs for PGAP3, GSDMB, and GSDMA, respectively. Most of the 41 SNPs identified by GWAS of asthma or autoimmune diseases (GWAS Catalog EMBL-EBI: www.ebi.ac.uk/gwas/) were also eQTL SNPs for PGAP3, GSDMB, or GSDMA, but showed opposite effect allele between asthma and autoimmune diseases. Higher expression levels of GSDMB were correlated with asthma (P = 0.05), higher number of exacerbations in last 12 months (P = 0.02), and higher reduction of ACQ6 after steroid treatment (P = 0.0008).

Conclusion: PGAP3, GSDMB, and GSDMA are potential functional genes in chr17q region for asthma. SNPs in GSDMB is associated with asthma and GSDMB expression levels, and its expression levels are correlated with asthma and asthma exacerbations, making it strong candidate gene for asthma. [SARP is funded by the NHLBI U10 HL109172, HL109168, HL109152, HL109257, HL109046, HL109250, HL109164, and HL109086].

OA0083 | Swimming pool training environment may drive skin and gut dysbiosis in elite swimmers

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Background: The effect of the training environment on human microbial communities has not been addressed before. Therefore, in this cross-sectional study, we aimed to assess skin and gut microbiome in elite swimmers compared with non-water competitive athletes.

Method: Skin and stool samples were collected from 29 elite swimmers and 34 soccer players using sterile nylon swabs. Skin samples were collected from the volar surface of the forearm of the participant's dominant side and stool samples by swabbing used bathroom tissue. The microbiome was profiled by 16S rRNA gene amplicon sequencing approach. Alpha diversity, which quantifies both species richness and evenness, was estimated with the inverse Simpson's index and compared between groups using Wilcoxon test. Beta diversity, which quantifies community composition similarity between samples, based on Bray-Curtis dissimilarity, was compared with adonis.

Results: In skin, the most common genera found among swimmers were *Enhydrobacter*, *Streptococcus*, *Halomonas*, *Shewanella* and *Streptococcus* and in non-water athletes were *Streptococcus*, *Staphylococcus*, *Enhydrobacter*, *Halomonas* and *Corynebacterium*. Swimmers had significantly lower alpha diversity (W = 557, P = 0.0272). Also, beta diversity was significantly different (R^2= 0.11, P < 0.01) between the two groups of athletes. Regarding to gut microbiome, the most common genera found were *Bacteroides*, *Faecalibacteium*, *Prevotella*, *Roseburia*. Nonetheless, *Lachnospiracea* and *Blautia* were increased in swimmers and *Ruminococcaceae* and *Bifidobacterium* in soccer players. Alpha diversity was similar (W = 309, P = 0.6066), for stool samples, however, beta diversity suggested a significantly community difference between swimmers and soccer players (R^2= 0.04, P = 0.03).

Conclusion: Our results suggest that training environment may have an important role in shaping human microbiome. Moreover, swimming pool training environment may drive skin and gut dysbiosis. These results emphasize the importance of training environment in the composition and diversity of microbiome, suggesting that adverse health effects may be mediated by changes on microbiota.

MONDAY, 3 JUNE 2019
OAS 15
CRS FROM BENCH TO BEDSIDE

OA0084 | Topographical diversity of the upper respiratory tract microbiome in chronic rhinosinusitis patients

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Background: The microbiome plays a potentially pivotal role in the pathology of chronic rhinosinusitis (CRS), though, the exact contribution to disease development and severity remains unclear. We here evaluated the microbiome in different niches of the upper respiratory tract (URT) of patients with CRS and compared it to the microbiome of healthy individuals. Additionally, we studied the correlation between the microbiome and different patient's characteristics, phenotypes and inflammatory markers.

Method: Nasal swabs were taken from the anterior nares, nasopharynx, maxillary sinus and ethmoid sinus from 225 CRS patients, during functional endoscopic sinus surgery (FESS). Nasal swabs from the anterior nares and nasopharynx from 100 healthy controls were taken during consultation. The microbiome was analyzed by 16S rRNA V4 Illumina sequencing. Bacterial diversity was evaluated by calculating the alpha diversity (richness and inverse Simpson) and beta diversity (Bray-Curtis similarity). Phenotype and patient's characteristics were documented via a questionnaire. Serum inflammatory markers, IL-5, IL-4, IL-13, IFN-γ and periostin, were measured using a multiplex assay and ELISA.

Results: Microbiome analysis from the sampled niches in CRS patients revealed that the anterior nares were most similar to the sinus microbiome (Bray-Curtis similarities of 0.57 with maxillary sinus and 0.6 with ethmoid sinus). Alpha diversity was significantly decreased in the anterior nares and nasopharynx in CRSsNP compared to controls (richness: $P = 0.002$; inverse Simpson index: $P = 0.0025$). No changes in alpha diversity was observed in CRSwNP compared to controls. *Dolosigranulum pigrum* was more prevalent in controls. *Corynebacterium tuberculostearicum*, *Haemophilus influenzae/aegyptius* and *Staphylococcus* taxa were more prevalent in CRS. An association between the microbiome features and history of FESS ($P = 0.043$), age ($P = 0.002$) and gender ($P = 0.005$) was also found. No correlations were found between any of the inflammatory markers and microbiome taxonomic profiles.

Conclusion: Bacterial diversity was reduced in patients with CRSsNP compared to CRSwNP and controls. A strong microbial continuity was observed between the sampled niches in CRS, of which the anterior nares were most representative for the sinus microbiome. Different new bacterial taxa were revealed as potential pathobionts in CRS. Further mechanistic studies are warranted to explore the role of these bacterial taxa in the pathology of CRS.

OA0085 | Broad immunoglobulin G repertoire in chronic rhinosinusitis with nasal polyps regulates pro-inflammatory IgE responses

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Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a condition characterized by local polyclonal IgE production. Local tissue IgE concentrations are often within the range of several thousand kU/L, consisting of functional polyclonal IgE-idiotypes. Despite elevated levels of IgE in nasal polyps, the regulatory mechanisms controlling IgE-mediated pro-inflammatory response remains to be fully investigated. Here, we assessed if locally induced IgG antibodies in the nasal polyps can inhibit IgE-mediated response.

Method: Levels of specific IgE were measured in nasal polyp homogenates of grass pollen allergics with CRSwNP (GPA, n = 6) and non-allergic controls (NAC, n = 6) by Immunosolid Allergen Chip Assay (ISAC). Nasal polyp homogenates were assessed for their capacity to promote IgE-facilitated allergen binding to B cells (IgE-FAB), basophil activation and histamine release. Local IgE and IgG repertoires were studied by Immunoglobulin 454 sequencing.

Results: We show that IgG plays a key role in controlling IgE-mediated inflammatory responses in nasal polyps. Nasal polyp homogenates from GPA, but not from NAC, was able to elicit a dose-dependent increase in allergen-IgE binding to CD23 on B cells (IgE-FAB). Depletion of IgG from nasal homogenates resulted in an increase in CD23-mediated IgE-facilitated allergen binding to B cells ($P < 0.05$), enhanced FcεRI-mediated allergen driven basophil activation and histamine release (all, $P < 0.05$). A similar response was observed in relation to specific IgE antibodies to Staphylococcus aureus (SE-IgE). The capacity of IgG in nasal polyps to limit IgE-mediated inflammation is based on the fact that IgG repertoires widely share the antigen targets with the IgE repertoires, in both allergic and non-allergic subjects.

Conclusion: Polyclonal IgE idiotypes in CRSwNP are functional, promote IgE-mediated pro-allergic inflammation and are partially antagonized by corresponding IgG-idiotypes. This is most likely due to the fact that IgE and IgG clonotypes are widely shared in nasal polyps.

OA0086 | IL-25 mediated Th2-biased inflammation in nasal polyps: role of respiratory virus infection and its modulation by interferon-alpha

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Background: Exacerbation of inflammatory airway diseases such as chronic rhinosinusitis with nasal polyps (CRSwNP) is often due to Th2-biased inflammation following a mis-regulation of upstream regulators such as IL-25. Respiratory virus infection is a major cause of the exacerbation of airway inflammation. We aim to investigate the relationship between respiratory virus infection and IL-25 induction in promoting nasal Th2-biased inflammation by the nasal epithelium, and the modulation of virus-IL-25 interaction using interferon-alpha (IFN-α).

Method: 60 nasal polyps (NP) and 40 non-NP control tissues were examined for their IL-25 expression. Subsequently, dispersed polyp cells (DPCs) were stimulated with recombinant IL-25 and/or IL-25 antibody to confirm IL-25 dependant Th2 cytokine production. To elucidate the interaction between respiratory virus infection and IL-25 production, human nasal epithelial cells (hNECs) were tested for their IL-25 expression following respiratory virus infection *in vitro*. The hNECs were then pretreated with recombinant IFN-α to examine its effects on viral induced IL-25 levels.

Results: Significantly increased levels of IL-25 were observed in NP tissues, and IL-25 transcripts positively correlated with computed tomography scores and the atopic status of CRSwNP patients. Flow cytometry analysis of DPCs showed IL-25 induced Th2 cytokines (IL-4, 5, and 13) production, which were blocked by IL-25 antibody. Elevated IL-25 transcript was observed in influenza-infected hNECs and significantly correlated with viral replication. IFN-α pretreatment prior to influenza infection in hNECs significantly reduced viral titers, resulting in reduced IL-25 expression.

Conclusion: We confirmed that increased IL-25 expression induced type 2 cytokines production in NP tissues. Similar induction of IL-25 during early influenza infection implicated virus infection as a potential risk factor contributing to NP pathogenesis, which may be ameliorated by low-dose IFN-α pretreatment.

OA0087 | Real-life assessment of chronic rhinosinusitis patients using mobile technology

Seys SF[1,2]; De Bont S[3]; Bousquet J[4]; Bachert C[5]; Fokkens WJ[6]; Agache I[7]; Bernal-Sprekelsen M[8]; Callebaut I[3]; Cardell L[9]; Carrie S[10]; Castelnuovo P[11]; Cathcart R[12]; Constantinidis J[13]; Cools L[3]; Cornet M[6]; Clement G[14]; De Sousa JC[15]; Cox T[16]; Deneyer L[2]; Doulaptsi M[17]; Gevaert P[5]; Hopkins C[18]; Hox V[19]; Hummel T[20]; Hosemann W[21]; Jacobs R[22]; Jorissen M[3]; Landis BN[23]; Leunig A[24]; Lund V[25]; Mariën G[2]; Mullol J[26]; Onerci M[27]; Palkonen S[28]; Proano I[28]; Prokopakis E[17]; Ryan D[29]; Riechelmann H[30]; Segboer C[6]; Speleman K[31]; Steinsvik A[32]; Surda P[18]; Tomazic P[33]; Vanderveken O[34]; Van Gerven L[3]; Van Zele T[5]; Verhaeghe B[35]; Vierstraete K[36]; Vlaminck S[37]; Pugin B[2]; Hellings PW[3]

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Background: Chronic rhinosinusitis (CRS) is a worldwide chronic respiratory disease associated with a significant socio-economic burden. Management guidelines are based on evidence generated by randomized controlled trials in selected patient populations, which sub-optimally reflects the real-life situation. Monitoring of patient-reported outcomes by mobile technology offers the capabilities to study real-life control and burden of CRS.

Method: This study reports on the evaluation of baseline data of the first 454 users of mySinusitisCoach (mSC), a mobile application for CRS patients. Patient profile characteristics of mSC users were assessed as well as the level of disease control based on EPOS criteria and VAS global symptom severity. Self-reported CRS phenotypes, treatment and impact of CRS on patient's daily life were analysed.

Results: Forty-seven percent of all CRS patients are uncontrolled based on evaluation of VAS global sinusitis symptoms and 61% based on EPOS criteria. Uncontrolled patients use mSC more frequently than well-controlled patients (16 vs 8 times, $P < .05$). The impact of CRS on sleep quality ($P < .0001$), lung symptoms ($P < .0001$) and daily life ($P < .0001$) is significantly higher in uncontrolled compared to well-controlled patients. CRSwNP show higher VAS levels for any of the symptoms ($P < .0001$) compared to CRSsNP. Half of patients showed a history of ESS (endoscopic sinus surgery), which significantly reduced global sinusitis symptoms ($P < .05$) and facial pain ($P < .05$).

Conclusion: Real-life data confirm the high burden of uncontrolled disease in CRS patients, which clearly impacts daily functioning of CRS patients. Revision sinus surgery improves patient-reported outcomes, but not in patients with a history of more than 3 procedures. Mobile technology opens a new era of real-life studies, which supports the evolution towards preventive and predictive.

OA0088 | Poor long-term effect of aspirin treatment on chronic rhinosinusitis with nasal polyps in patients with NSAID- exacerbated respiratory disease

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Background: Non-steroidal anti-inflammatory drug (NSAID) exacerbated respiratory disease (N-ERD) is a clinical syndrome usually including a triad of chronic rhinosinusitis with nasal polyposis (CRSwNP), asthma and Acetylsalicylic acid (ASA) intolerance. ASA desensitization (AD) followed by ASA treatment after desensitization (ATAD) are considered in the management of N-ERD when maximal medical therapy added by recurrent sinus surgery is not sufficient for disease control. There is limited knowledge of the effect of AD. The aim of this retrospective cohort study was to evaluate the effect of AD on disease control in patients with N-ERD .

Method: Data of N-ERD patients (N = 145) undergoing surgical consultation for their chronic rhinosinusitis (CRS) in Helsinki, Tampere and Kuopio University Hospitals 2001-17 were used. All patients undergoing ATAD (n = 78) were included, and a random sample of severe CRSwNP+N-ERD patients (n = 67) without ATAD served as a control group. Patient characteristics, the information of current CRS-surgery, ATAD, and follow-up data (in 2018) were collected from patient records. Discontinuation of ATAD, revision CRS-surgery during the follow-up, prescribed and bought courses of systemic corticosteroids and antibiotics for airway infections during the years 2016-17, were used as outcome measurements. Associations were analyzed by survival and nonparametric methods.

Results: Compared to those who did not undergo ATAD, the ATAD group had higher tissue eosinophilia, reported more symptoms, and had a higher number of previous CRS-surgeries (median 1 vs. 2, $P < .001$). The discontinuation rate was 41 %, independent of dose or duration of ATAD. The most frequently reported reasons of discontinuation were side-effects and/or lack of effect. ATAD did not affect revision CRS surgery rate or peroral corticosteroid use during the follow-up. ASA mg*years had poor predictive potential of controlled over uncontrolled CRSwNP (AUROC < 0.63, $P > .05$). ASA > 100 mg users bought slightly less antibiotic courses during the follow-up compared to those using ASA ≤ 100 mg per day.

Conclusion: Compared to controls, ATAD did not affect revision CRS-surgery rate, or need of peroral corticosteroids or antibiotic courses during the follow-up. Slight decrease of antibiotic use was detected in those who were able to continue ASA > 100 mg daily. Prospective controlled studies are needed to evaluate the effect and risks of ATAD.

OA0089 | Dupilumab efficacy in patients with severe chronic rhinosinusitis with nasal polyposis: Pooled results from the SINUS-24 and SINUS-52 phase 3 studies

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Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic type 2 inflammatory disease with a high symptom burden and poor quality of life. Dupilumab (DPL), a fully human mAb blocking the shared receptor component for IL-4 and IL-13, key drivers of type 2-mediated inflammation, is approved for inadequately controlled moderate-to-severe atopic dermatitis in adults, and in the USA for patients (pts) aged ≥ 12 years with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma. Its efficacy and safety were evaluated in pts with severe CRSwNP in 2 large phase 3 studies—SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454). We report results from the pooled analyses of these 2 randomized, double-blind, placebo (PBO)-controlled studies, evaluating DPL efficacy vs PBO after 24 weeks of treatment in pts with severe CRSwNP previously treated with systemic corticosteroids and/or surgery and receiving mometasone furoate nasal spray (MFNS) and standard of care.

Method: SINUS-24 pts were randomized 1:1 to subcutaneous (SC) DPL 300 mg or PBO every 2 weeks (q2w) for 24 weeks. SINUS-52 pts were randomized 1:1:1 to SC DPL 300 mg q2w for 52 weeks, DPL 300 mg q2w for 24 weeks followed by 300 mg every 4 weeks for 28 weeks, or PBO q2w for 52 weeks. The results of change from baseline to Week 24 in nasal polyp score (NPS), patient-reported nasal congestion (NC), sinus CT Lund–Mackay (CT-LMK), total symptom score (TSS), UPSIT smell test, daily loss of smell, and SNOT-22 scores from all pts randomized to DPL 300 mg q2w (n = 438) vs PBO (n = 286) were pooled.

Results: Baseline disease characteristics were comparable between groups. DPL significantly improved NPS, NC, CT-LMK, TSS, UPSIT, daily loss of smell, and SNOT-22 scores (all $P < .0001$ vs PBO) (Table). Common adverse events (in ≥ 5% pts) were nasopharyngitis, nasal polyps, headache, asthma, epistaxis, and injection-site erythema, all occurring with higher frequency in PBO-treated pts.

Conclusion: DPL as add-on to MFNS significantly improved endoscopic, clinical, radiological, and patient-reported outcomes vs MFNS alone after 24 weeks in pts with CRSwNP in the pooled SINUS-24/SINUS-52 population and was well tolerated.

Change in score from baseline to Week 24, LS mean	NPS[a]	NC[a]	CT-LMK[a]	TSS[a]	UPSIT[b]	Daily loss of smell[a]	SNOT-22[a]
Placebo (n = 286)	0.12	−0.42	−0.16	−1.08	−0.03	−0.26	−10.36
Dupilumab 300 mg q2w (n = 438)	−1.79	−1.30	−6.27	−3.59	10.54	−1.30	−29.22
LS mean difference vs placebo (P value)	−1.91 (<.0001)	−0.88 (<.0001)	−6.12 (<.0001)	−2.52 (<.0001)	10.57 (<.0001)	−1.04 (<.0001)	−18.86 (<.0001)

[a] Higher mean scores for NPS (scored 0–8), NC (0–3), CT-LMK (0–24), TSS (0–9), daily loss of smell (0–3), and SNOT-22 (0–110) indicate more severe disease. [b]For UPSIT (scored 0–40), lower mean score indicates more severe disease.
LS, least squares.

MONDAY, 3 JUNE 2019
OAS 16
STRATEGIES TO REDUCE THE IMPACT OF ALLERGIC DISEASE

OA0090 | Impact of allergic diseases at the emergency room in Padua University Hospital during the decade 2008-2017

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Background: The increase of allergies implies a high impact on the Emergency Room (ER) in terms of epidemiology and resource use. This retrospective observational study aims to assess the impact of allergic diseases at the ER of the General Hospital—University of Padua (GHUPD) from 2008 to 2017.

Method: Allergic reactions were divided into 7 subclasses: rhinoconjunctivitis, asthma, urticaria/angioedema, isolated angioedema, dermatitis, anaphylaxis and anaphylactic shock. We identified 63 ICD-9-CM nosological codes potentially related to allergies. We read the discharging reports and found that 10.286 consisted in allergic manifestations. The parameters (prevalence of allergies compared to total admissions, symptoms, gender, age, mode of arrival, triage code, recovery duration, history of allergies, etiology, blood tests, consultations, therapy and drugs prescribed) were analysed by SAS 9.2 program for Windows and statistical analyses were performed by test of hypothesis $\chi 2$ and Fisher's exact test.

Results: Allergic diseases, which accounted for 1.20% of total admissions at the ER of GHUPD were distributed as follows: 46.43% urticaria/angioedema, 21.58% asthma, 15.66% dermatitis, 12.37% isolated angioedema, 2.94% anaphylaxis, 0.66% anaphylactic shock and 0.37% rhinoconjunctivitis. Differences between allergies and overall admissions resulted statistically significant ($P < .001$) for age, sex, triage codes, mode of arrival, and clinical outcome. A greater attribution of red/yellow codes to allergic reactions was observed, as well as a prevalence in the female gender and younger population. History of allergies and a putative etiologic factors were respectively reported in about 66% and 52% of cases. The drugs most commonly used were found to be corticosteroids (70.95%) and antihistamines (58.93%), whilst epinephrine had been administered in 82.09% of anaphylactic shocks and in 27.33% of anaphylaxes. 65.84% of the patients were evaluated by a specialist on admission or within 72 hours. The Short-term Intensive Observation (STIO) showed to be a modality more prevalent in allergies than in global accesses (9.53 vs. 5.58%, $P < .001$), with a low percentage of hospitalizations for allergies.

Conclusion: Our data demonstrate a significant impact of allergies' management on the ER both in terms of patient numbers and resource use. STIO appeared to be an appropriate strategy to reduce hospital stays even in the most acute cases, while ensuring an adequate period of time for monitoring clinical evolution.

OA0091 | Awareness of 119 (911) rescue team on anaphylaxis and asthma exacerbations in Korea: Before and after the education

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Background: Anaphylaxis and asthma exacerbation could be life-threatening medical emergency in allergy. 119 (911 in USA) rescue teams are at the forefront of such emergency conditions. Early recognition and proper prehospital managements by 119 rescuers is important. We evaluated the awareness of 119 rescuers on anaphylaxis and asthma exacerbation in Korea.

Method: From May 17 to June 28, 2018, a total of 195 rescuers were recruited from Gyeonggi province, Korea. The 3-hour educational sessions on anaphylaxis and asthma exacerbation were provided 4 times by an allergy specialist including lectures and hands-on workshop on self-injectable epinephrine autoinjector. Each time about 23~60 rescuers attended. Questionnaire survey with the same content was done before and after the education to assess the improvement of the awareness. The questionnaire had three domains: anaphylaxis awareness assessment, asthma awareness assessment, and program satisfaction assessment.

Results: After excluding the 15 who did not submit the questionnaire, total 180 rescuers were included. After education, awareness score about anaphylaxis was increased from an average of 40 to 82.9. Particularly, the effect of education on the use of epinephrine, the most crucial treatment for anaphylaxis, was greatest. However, the percentage of correct answers to the question of 'when epinephrine autoinjector should be administered' was 66.9% before and 54.4% after education. The awareness score of asthma after education increased from an average of 82.5 to 92.5. The suitability of education time and level, utilization of education contents, satisfactions with lecture program and training program were all almost 100%.

Conclusion: 119 rescuers could be the first persons at the forefront of anaphylaxis and asthma exacerbation. It is important to increase their awareness on anaphylaxis and asthma exacerbation. Simple educational activity can dramatically change the level of the awareness.

OA0092 | Psychological factors associated with quality of life and burden in parents of children with food allergy

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Background: Studies have identified that food allergy (FA) in children is related to poor parental quality of life (QoL) and mental health. Furthermore, there is evidence that QoL may be lower for parents of children with FA than parents of children with other chronic health conditions. However, there is a paucity of evidence exploring psychological factors associated with QoL and burden of parents of children with FA which this study aims to address.

Method: Baseline data from a randomised controlled trial of an online self-help intervention for parents of children with FA were used for the analysis. Demographics in addition to the dependent variable (Food Allergy Quality of Life-Parental Burden (FAQL-PB)) and independent variables (depression, anxiety, stress, intolerance of uncertainty and self-efficacy) were collected.

Results: A total of 205 parents completed the baseline questionnaires (97% female, mean age 38.95 years (SD = 6.89)). Initial analysis revealed that all independent variables significantly correlated with FAQL-PB (*ps* < .001). Stepwise multiple regression was used to determine if all proposed psychological factors significantly contributed to FAQL-PB. The results of the regression indicated that two psychological factors contributed to 37.1% variance in FAQL-PB (R^2=.37, F(2,202) = 61.07, *P* < .001). It was found that anxiety significantly contributed to FAQL-PB (β=.39, *P* < .001) as did self-efficacy (β=-.38, *P* < .001). Depression, stress and intolerance of uncertainty were not found to contribute to variance explained.

Conclusion: This study identifies that parental generalised anxiety and inadequate feelings of self-efficacy associated with poorer QoL and burden for parents of children with FA. Surprisingly, depression, stress and intolerance of uncertainty were not found to be related to parental QoL and burden indicating that interventions should be targeted at improving anxious and efficacious thoughts and behaviours. This is particularly important given the evidence that parental anxiety related to anaphylaxis can be transferred to the child which may affect the child's longer-term outcomes if not addressed.

OA0093 | Sequential nut oral food challenges improve the quality of life of nut-allergic children

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Background: Nut allergies are common in children and often associated with dietary eviction of all nuts. The aim of this study was to determine whether sequential oral food challenges (OFCs) to nuts and introduction of tolerated nuts improves the overall quality of life of both children and parents.

Method: Nut-allergic children 1 to 16 years of age were recruited in 3 European centers: Geneva, London, and Valencia. Health related quality of life (HRQL) assessment was performed using the validated food allergy quality of life questionnaire parent form (FAQLQ-PF) and the validated FAQLQ child form (FAQLQ-CF) in children 7 to 12 years before the sequential OFCs and after 1 year. Data were analyzed using a two-tailed Wilcoxon signed-rank test for paired samples and a Wilcoxon rank-sum test for independent samples.

Results: Sixty-nine parents and 13 children (aged 7-12 years) filled out the HRQL questionnaires. There was a statistically significant improvement in mean FAQLQ-PF score (2.65 to 2.34; *P* = .025) and mean FAQLQ-CF score (3.71 to 2.80; *P* = .0078) at 1 year follow-up. However, mean FAQLQ-PF score was not improved in children with higher number of clinical reactions (≥ 5) during sequential OFCs (n = 10, 2.56 to 3.02, *P* = .11). These children had higher mean baseline index nut specific IgE compared to the rest of the cohort (53 vs 27 kU/L, ImmunoCAP, *P* = .02).

Conclusion: Despite a significant time and resource investment, sequential nut oral food challenges improved the quality of life in the majority of patients with nut allergies, although this was not the case for patients with a large number of reactions on consecutive OFCs.

OA0094 | Long-term longitudinal impact of probiotic peanut oral immunotherapy (PPOIT) on patient quality of life at 4 years post-treatment

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Background: Probiotic peanut oral immunotherapy (PPOIT) was previously shown to improve Food Allergy Quality of Life (FAQLQ) of children with peanut allergy from baseline to 12 months post-treatment. We examined if improved FAQLQ is maintained to 4 years post-treatment and factors that predict long-term FAQLQ.

Method: Participants in the PPOIT randomised trial with completed FAQLQ at all 5 time points were included: T0 (pre-treatment), T1 (end-of-treatment), T3, T4, T5 (3, 12 months and 4 years post-treatment, respectively). Within- and between-group changes were examined for FAQLQ and FAIM using Paired t-tests and multivariate analysis, respectively. Linear regression examined for predictors of FAQLQ at 4 years post-treatment.

Results: N = 38 parents of children 1-10 years at enrolment (19 Placebo/19 PPOIT) completed FAQLQ at all 5 time points. Multivariate analysis showed that FAQLQ improved significantly only for the PPOIT group ($F = 6.1$, $P = .001$). Paired tests showed that FAQLQ improvement increased for the PPOIT group from T3 through T4 to T5, with margin of improvement reducing as optimal HRQL was reached. Similar improvement in FAIM over time was observed ($P = .001$). At T5, a "large" amount of peanut ingestion ($P = .02$) predicted a greater improvement in long-term FAQLQ score, compared with no, small or moderate ingestion amounts, controlling for DBPCFC outcome. For placebo subjects, FAQLQ and FAIM remained similar to baseline at T3, T4 and T5.

Conclusion: PPOIT-induced improvement in FAQLQ was maintained to 4 years post-treatment. Greatest benefit was conferred by an ability to ingest large amounts of peanut rather than more limited intake or continued avoidance.

TABLE 1 Change in FAQLQ score T0 to T5 according to amount of peanut protein ingested for PPOIT.

Amount of peanut ingested at T5	Change
Placebo	−0.2
None	−1.2
Small	−1.7
Moderate	−2.4
Large	−2.6
$y = -1.52\ln(x) - 0.1647$, $R^2 = .9904$	

OA0095 | Management of allergic rhinitis in community pharmacy—A systematic literature review

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Background: Allergic rhinitis (AR) is a high prevalent disease with symptoms that can severely affect patient's everyday life. Community pharmacists may contribute to symptom identification and medication recommendation aiming to control AR's symptoms. The present systematic review aims to collect interventions in community pharmacy regarding AR in order to better understand pharmacist's role in identifying AR's symptoms, counselling about the right treatment and monitor patient's outcomes and quality of life.

Method: A literature search was performed on three different electronic databases, PubMed, Web of Science and Cochrane Central Register of Controlled Trials, aiming to find potentially relevant articles related to the intervention of community pharmacists on AR management, published from January 2000 to November 2018.

Results: From the literature search performed, 20 citations fulfilled the inclusion criteria. Through the evaluation of these citations, it was possible to verify that most patients self-manage their disease with over the counter (OTC) medication, presenting a sub-optimal control of AR's symptoms, with many not having a disease diagnose. In the studies in which the quality of patients' lives was evaluated before and after community pharmacist's intervention, it was possible to verify a significant improvement of this parameter, as well as symptom amelioration and compliance improvement, resulting in a better disease management. Additionally, a study concluded that the use of a computerized decision support system may further improve pharmacist's intervention. Despite these positive results, pharmacist's knowledge regarding ARIA guidelines is scarce. Information leaflets regarding AR available in community pharmacies exhibit, in its majority, poor scientific quality and frequent errors.

Conclusion: Pharmacists can have a crucial role in helping patients manage their AR symptoms, counsel them about instituted treatment and monitoring its outcomes, being able to significantly improve patient's quality of life, maximize the benefits of AR treatment and reduce direct and indirect costs related to the disease. Because only a small number of studies exist concerning community pharmacist's intervention on AR, more studies need to be conducted.

OA0096 | Does grandmother's smoking influence asthma risk in the grandchild? A systematic review and meta-analysis

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Background: While maternal smoking during pregnancy increases asthma risk in the offspring, it has been suggested that the effect may extend even to the grandmother's smoking. Some studies have investigated the transgenerational effect of grandmother's smoking on grandchild's asthma, but findings are inconsistent. We synthesized evidence from studies that investigated the association of maternal or paternal grandmother's smoking with asthma risk in the grandchild. We also sought to understand whether this effect differs by sex of the grandchild.
Method: We searched MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, CAB International and WHO Global Health Library, Global Health, CINAHL, PsycINFO, Scopus, Google Scholar and Zetoc for observational epidemiological studies on the topic. The last search was conducted on December 30, 2018. Two reviewers independently screened records, extracted study data, and appraised the quality of included studies using the Effective Public Health Practice Project tool. We used random-effects meta-analysis to quantitatively combine study estimates.
Results: One nested case-control and five cohort studies with 114,931 grandmother-child pairs were included. Two studies were rated as moderate and four as strong quality. Maternal grandmother's smoking during pregnancy was significantly associated with an increased risk of asthma (OR 1.25, 95%CI 1.06-1.47 [4 studies]; RR 1.22, 95%CI 1.10-1.36 [2 studies]) in the grandchild. The risk was greater when the child's mother also smoked when pregnant with the child (OR 1.85, 95%CI 1.03-3.30 [2 studies]) than when she did not smoke (RR 1.30, 95% CI 0.94-1.79 [3 studies]). Paternal grandmother's smoking was not associated with grandchild's asthma (OR 1.04, 95% CI 0.91-1.20 [2 studies]). Results were inconsistent across studies as to whether the effect of grandmother's smoking on asthma differed by the grandchild's sex.
Conclusion: Maternal grandmother's smoking, but not that of the paternal grandmother, during pregnancy is associated with an increased risk of asthma in the grandchild. The risk was greater if the child's mother also smoked during pregnancy than if she did not smoke during pregnancy. We found no evidence that this risk differs by the sex of the grandchild. Epigenetic alteration from tobacco exposure might explain this transgenerational effect.

OA0097 | High-dose vitamin D supplementation during pregnancy and asthma at age 6: A randomized controlled trial

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Background: Recent double-blind randomized clinical trials (DB-RCTs) have shown that prenatal high-dose vitamin D supplementation reduces risk of wheezing illnesses in the offspring in the first 3 years of life, but the long-term effect on asthma is unknown.
Here, we aimed to investigate if supplementation of vitamin D during pregnancy affects risk of asthma and related traits in the offspring by age 6.
Method: A single-center DB-RCT embedded in the Copenhagen Prospective Study on Asthma in Childhood 2010 (COPSAC2010) cohort with persistent wheeze through age 3 as primary outcome. We enrolled 623 women at pregnancy week 24 beginning in March 2009. The 6-year follow-up of the children (N = 545) was completed in March 2017.
315 women were randomized to receive daily 2400 IU vitamin D and 308 women were randomized to receive placebo. All women additionally received the recommended 400 IU/d of vitamin D.
Primary outcome was current asthma at age 6 diagnosed based on a day-to-day symptom diary, regular scheduled and acute clinic visits, and response to inhaled corticosteroid with relapse at withdrawal. Secondary outcomes were lung function, bronchial reactivity to methacholine, fractional exhaled nitric oxide, allergic sensitization and rhinitis at age 6.
ClinicalTrials.gov identifier: NCT00856947.
Results: The high-dose vs. standard dose of vitamin D supplementation during pregnancy did not affect the risk of asthma by age 6: no./total no. (%), 23/274 (8%) vs. 18/268 (7%), odds ratio (OR) = 1.27 [95% CI, 0.67–2.42], *P* = .46, the age at onset of persistent wheeze/asthma: hazard ratio (HR) = 0.90 [0.64–1.28], *P* = .56, or the yearly prevalence of persistent wheeze/asthma at age 1-6 year: OR = 0.87 [0.59–1.28], *P* = .48. There were no effects on lung function, bronchial reactivity or allergy outcomes at age 6.
Conclusion: A 7-fold increased daily dose of vitamin D during the third trimester of pregnancy did not reduce the offspring's risk of asthma or allergic sensitization by age 6 years.

OA0098 | Efficacy of inhaled salbutamol with and without prednisolone for first acute rhinovirus-induced wheezing episode

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Background: Acute rhinovirus-induced wheezing is common in young children and may respond to a short-course of systemic corticosteroid. There are no trials on the efficacy of inhaled beta$_2$-agonist in this clinical scenario. Our aim was to study the short-term efficacy of inhaled beta$_2$-agonist with and without oral corticosteroid in the first acute rhinovirus-induced severe wheezing episode in young children.

Method: The study population was formed from two randomized trials comparing oral prednisolone (2 mg/kg/d for 3 days) to placebo: Vinku (n = 35/293, NCT00494624) used high-dose nebulized salbutamol (first 12 h 0.15 mg/kg q2 h, then q4 h) and Vinku2 (n = 60/124, NCT00731575) used on-demand inhaled salbutamol during hospitalization. Both trials had follow-up at 2 months. Rhinovirus was detected by PCR. Unadjusted analysis focused on four treatment groups: salbutamol high-dose/prednisolone *vs.* salbutamol on-demand/prednisolone *vs.* salbutamol high-dose/no prednisolone *vs.* salbutamol on-demand/no prednisolone.

Results: The median age of the 95 eligible subjects was 13 months (IQR, 8-17 months). Baseline characteristics were similar across groups. However, the treatment groups differed according to median time until discharge (18, not applicable [due to delay in randomization], 18, and 21 hours, respectively; overall $P = .02$), duration of cough (4, 13, 6, and 16 days; $P < .001$), new physician-confirmed wheezing episode (13%, 50%, 53%, and 37%; $P = .056$); and rehospitalization due to wheezing (0%, 7%, 33%, and 17%; $P = .04$).

Conclusion: The combination of high-dose inhaled salbutamol and oral prednisolone appears most beneficial in young children with first rhinovirus-induced severe wheezing episode.

OA0099 | Tiotropium a new treatment option for severe uncontrolled pre-school asthma

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Background: Current guidelines recommend inhaled corticosteroids (ICS) and/or montelukast in pre-school asthma as there is insufficient data available on treatment with inhaled corticosteroid (ICS) + long acting-ß-agonist (LABA) combinations or a modern [ICS+LABA +long acting muscarin receptor antagonist (LAMA)] triple therapy in young children.

Method: A retrospective analysis of the electronic medical records of the pneumological ambulance in Frankfurt was performed in 2017. Prescriptions were analyzed and asthma control evaluated. Using a case-control design, we compared 20 children with not well-controlled symptoms who had a history of severe asthma, to 40 healthy controls (age 1-5 years) matched by age, and sex. Moderate and severe asthma exacerbations and health utilization were analyzed 6 months before and 6 months after adding a LAMA (Tiotropium). In addition, treatment success was estimated by parents using a Likert scale.

Results: In 2017, 2184 patients aged 0-18 years were treated in our out-patient department. Of these, 934 (42.7%) were < 6 years old. The diagnosis of pre-school asthma was made 436 times. The prescriptions were as follows: Montelukast 44.7%; ICS + LABA 36.8%; ICS Mono 14.1% and ICS + LABA + LAMA therapy in 4.8%. Twenty one (4.8%) uncontrolled severe cases were switched to an ICS + LABA + LAMA (triple therapy). The physicians assessment was clear: Asthma control (moderate and severe asthma exacerbations) during triple treatment was significantly better than in the previous 6 months without adding a LAMA. Parents were fully satisfied and health utilization decreased to the level of controls.

Conclusion: Our retrospective study showed that adding tiotropium is a new treatment option for patients with severe pre-school asthma. A 3-arm prospective double-blind study (ICS vs. ICS + LABA vs. ICS + LABA + LAMA) over 6 months in pre-school asthma is urgently needed to adapt current guidelines to modern care reality.

OA0100 | The effect of polivalent mechanical bacterial lysate on the clinical course of pollen allergic rhinitis in children

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Background: Due to the high incidence of seasonal allergic rhinitis (SAR), the negative impact of the disease on the quality of life, and the incomplete effectiveness of available types of therapy, new treatment methods are being developed. Industry literature and the results of our own study conducted in 2017 suggests that bacterial lysates may be one of the options.

Method: The study was a prospective, randomized, double-blind, placebo-controlled study. 63 children with SAR caused by grass pollen were enrolled in the study. 34 children received polyvalent mechanical

TABLE 1 TNSS and TOSS in four periods of the grass pollen season.

	PMBL group					Placebo group					
	T_0	T_1	T_2	T_3	*P*-value		T_0	T_1	T_2	T_3	*P*-value
TNSS	2.63	3.35	2.29*	1.63*	<.01	TNSS	2.76	3.8	4.34*	3.48*	>.05
TOSS	0.71	0.95	0.65	0.33	<.05	TOSS	0.69	0.68	0.85	0.59	>.05

TABLE 2 PNIF and the results of additional tests performed during the three visits.

	PMBL group					Placebo group			
	V1	V2	V3	*P*-value		V1	V2	V3	*P*-value
PNIF	99.26	111.03	118.68*	<.05	PNIF	104.83	98.83	92.62*	>.05
Nasal eosinophils	0.07	0.41*	0.34*	<.001	Nasal eosinophils	0.06	0.56*	0.47*	<.001
asIgE concn.	0.38	0.43	0.37	>.05	asIgE concn.	0.28	0.39	0.7	<.05

bacterial lysate (PMBL) during the grass pollen season (May-July 2018), sublingually for 10 consecutive days each month for 3 consecutive months, the remaining patients (n = 29) received the placebo.

SAR symptoms were recorded by parents of children in the daily patient diary according to the standard scoring systems (TNSS—total nasal symptom score, TOSS—total ocular symptom score). At each of the three visits (V1– at the beginning, V2– at the peak, V3– at the end of the grass pollen season), the peak nasal inspiratory flow (PNIF) was measured. Nasal swabs for the presence of eosinophils and nasal lavage for the presence of specific IgE (asIgE) against Timothy-grass pollen allergens were taken from the patients. The average values of TNSS, TOSS obtained from four seven-day periods of the grass pollen season (T0–T3), PNIF values, and the results of additional tests from each visit were used for statistical analysis.

Results: In the tables, the data is expressed as the arithmetic mean. Statistically significant differences between the compared groups are marked with an asterisk.

Conclusion: This is the first RDBPC study which has demonstrated that PMBL was able to significantly improve nasal and ocular symptoms of SAR in children and limit the increase in the number of eosinophils in nasal swabs.

OA0101 | Immune, microbial, atopic characteristics and epithelial integrity in children with adenoid hypertrophy

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Background: Childhood is connected with the gradual maturation of systemic and mucosal immunity and one of the consequences of such immune immaturity are the recurrent respiratory tract infections. One of the most common forms of chronic focal infections leading to many health consequences is adenoid hypertrophy (AH). The connection between adenoid hypertrophy and immune system is bidirectional. Immune immaturity and recurrent infections lead to the chronic stimulation of mucosa-associated lymphoid tissue of the upper airways and vice versa, adenoid hypertrophy causes airway mechanical obstruction and deterioration of mucosal clearance, thus increasing the susceptibility to infections and mucosal immune system defects.

Method: We analyzed the characteristics of immune system and atopic status of the children with AH requiring adenoidectomy. Altogether, 72 children with AH (48 boys, 66.7%; aged 4.5 ± 2.2 years) and 17 healthy children were included. E-cadherin concentration in peripheral blood was evaluated as a marker of epithelial integrity.

Results: Results of the cellular immunity did not show any significant deviations, however, 6 months after surgery, lymphocytes number declined to normal values. IgG1, IgG2, total IgE and complement components (C3 and C4) were significantly increased. In 19% of the children, complete mannose-binding lectin deficiency (MBL) was detected. Atopy was detected in 83% children. The majority of them were sensitized against house dust mite and cat dander. Atopy and passive smoking showed deteriorating effects on the parameters of systemic humoral immunity and supported the airway colonization by pathogenic bacteria. Moreover, passive smoking and sensitization to HDM were associated with increased concentration of E-cadherin in peripheral blood.

Conclusion: Immune system is affected by chronic antigenic stimulation in children with adenoid hypertrophy. Surgical removal of AH normalized immune functions. Moreover, atopy and passive smoking could be considered as important risk factors for AH development and negative changes in mucosal microbiome. Passive smoking and sensitization against perennial allergens are associated with disturbed airways epithelial integrity expressed by increased concentration of E-cadherin in the blood.

MONDAY, 3 JUNE 2019
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ALLERGEN IMMUNOTHERAPY: MECHANISMS AND BIOMARKERS

OA0102 | MiR-8485 is locally upregulated upon allergen-specific immunotherapy and coincides with shifted Breg/Th17 balance

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Background: IL-10-producing regulatory B cells (Bregs) are known to maintain regulatory capacities of T cells; on the other hand, they also inhibit effector Th17 differentiation. In our recent study, we found systemic changes of Breg frequencies, with a mirror-inverted course compared to effector Th17 cells during grass pollen-specific immunotherapy (AIT). In addition, a transitory Treg population, characterized by the simultaneous expression of FoxP3 and IL-17, showed significant changes during AIT. In the current study, we aimed to analyze this AIT-specific balance shift between regulatory and effector immune cells in the local sputum environment and, at the same time, study the impact of RNA interference.

Method: Induced sputum and PBMCs were collected from patients suffering from allergic rhinitis patients with (AA: n = 20) and without asthma (AR: n = 15) as well as from healthy subjects (n = 24). Allergic patients with (n = 8) and without AIT (n = 7) as well as asthmatic patients with (n = 11) and without (n = 9) AIT were included. Systemic and sputum T and B cell subsets were analyzed by flow cytometry. MicroRNA (miR) expression was detected using a human miR microarray.

Results: Our data show that IL-10-producing Bregs were significantly increased upon AIT, in blood and sputum from allergic patients. The local effect coincided with a significant decrease of effector Th17 cells, and, notably, with an increase in the transitory IL-17$^+$FoxP3$^+$CD4$^+$ population. Further, we found several miRs, which were regulated in a differential manner in sputum cells upon treatment. In particular, miR-8485 stands out, which is significantly upregulated following AIT in AR as well as AA patients. This miR carries the potential to dampen the expression of CD19, CD2-associated protein, CD3e, IL17RA, IL17F, IL13 and more.

Conclusion: Here, we describe a congruence of local miR expression in sputum cells and according to frequencies of effector T- and regulatory B-cell subsets. Upon AIT, miR-8485 has the potential to dampen immunological factors involved in the pathological mechanism of allergic asthma. In conclusion, our data hint to a so far unknown AIT mechanism involving RNA interference.

OA0103 | Epigenetic changes in SATB1 gene in FoxP3 + regulatory T cells reflect immune tolerance status during grass pollen subcutaneous and sublingual immunotherapy

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Background: Regulatory T cells (Tregs) play an indispensable role in immune tolerance induction during allergen immunotherapy (AIT) which can be administered either subcutaneously (SCIT) or sublingually (SLIT). Recently, a T lineage-enriched transcription factor, special AT-rich sequence binding protein-1 (SATB1), has been reported as a functional marker of Tregs. We hypothesised that FoxP3$^+$ Treg cells are dysregulated in grass pollen allergic subjects (SAR) and their functional activity following SCIT and SLIT is restored when SATB1 is repressed in Tregs. Furthermore, the SATB1 gene is differentially methylated between the SAR and AIT-treated patients.

Method: In a prospective, controlled study of AIT, conducted during the pollen season, peripheral blood mononuclear cells were obtained from SCIT (n = 12), SLIT (n = 12), those who completed 3 years of SLIT (SLIT-TOL; n = 6), SAR (n = 24), and non-atopic controls (NAC) (n = 24). FoxP3$^+$ and SATB1$^+$FoxP3$^+$ Tregs were enumerated by flow cytometry and then confirmed by qRT-PCR. Additionally, a genome-wide DNA methylation analysis was performed on Tregs and Tconv cells across all patient groups.

Results: SCIT, SLIT and SLIT-TOL groups had lower rhinoconjunctivitis symptom scores compared to SAR (all, $P < .05$). The proportion of FoxP3$^+$Tregs was significantly lower in SAR compared to NAC ($P < .001$). However, there were no differences in FoxP3$^+$ Tregs in SCIT, SLIT and SLIT-TOL groups when compared with SAR. In contrast, a higher proportion of SATB1$^+$FoxP3$^+$ Tregs were observed in SAR compared to NAC ($P < .001$) and a significantly lower proportion in SCIT, SLIT and SLIT-TOL groups (all, $P < .001$). SATB1 mRNA expression was downregulated in SCIT, SLIT and SLIT-TOL groups (all, $P < .001$) when compared to the SAR group. Functional analysis demonstrated a significant reduction in the suppressive capacity of FoxP3$^+$ Tregs in SAR compared to SCIT, SLIT and SLIT-TOL groups (all, $P < .05$). Methylation of the FoxP3 gene did not reveal any differential methylation between patient group, however, the SATB1 gene was significantly unmethylated in SAR compared with NA and methylated in AIT-treated groups ($P < .05$).

Conclusion: For the first time, we report that SATB1 expression is reduced in FoxP3$^+$Tregs following AIT and that SATB1 is

differentially methylated between SAR and AIT-treated groups. Furthermore, SATB1 expression was associated with successful AIT, highlighting its potential role as a novel molecular biomarker of AIT tolerance.

OA0104 | The frequency of allergen-specific T regulatory cells before AIT is associated with treatment response

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Background: Allergen-specific immunotherapy (AIT) represents the only curative treatment of allergic diseases. Although recent research provides strong evidence on pivotal mechanisms of AIT the robust biomarkers assisting the efficacy monitoring or stratification of best responders before treatment still need both validation and qualification.
Method: Clinical trial design and outcomes have been previously published. Peripheral blood mononuclear cells (PBMCs) were collected from birch pollen allergic patients before, during and after AIT with COPs from *Bet v1*. PBMCs were cryopreserved and following resuscitation were stimulated in batches with recombinant Bet v 1 for 7 days. Frequencies of Th1, Th2, Treg cells were measured using flow cytometry. Secreted cytokine levels in culture supernatants were determined using Bioplex kits.
Results: In this study, we investigated changes in T cell subset frequency before and during the course of AIT in a double-blind, placebo-controlled phase IIb study in birch pollen allergic patients (NCT02271009). Here we show that antigen-specific T regulatory cell frequency increases in both responder and non-responders. However, the magnitude of change from baseline was significantly greater in the responder group. This might be due to the significantly lower levels of T-regulatory cells in the responders measured at the baseline.
Conclusion: Patients with the lowest levels of T regulatory cells, or who are deficient in T regulatory cells, are more likely to benefit the most from an increase in circulating T regulatory cells. These findings also suggest that the subset of $Treg^{low}$ birch pollen allergic patients should be targeted and encouraged to undergo AIT.

OA0105 | Der P 23 shows limited IgE diagnostic value and does not appear to impact clinical outcomes of HDM sublingual allergy immunotherapy

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Background: Der p 23 (Dp23) has recently been identified as a major house dust mite (HDM) allergen based on high IgE sensitisation frequencies in different populations. The objectives of this *post-hoc* analysis were to examine the diagnostic value of Dp23 for assessing HDM allergic sensitisation and to examine the immunological and clinical effects of HDM sublingual allergy immunotherapy (SLIT) in relation to Dp23 sensitisation status.
Method: Der p 1 (Dp1), Der p 2 (Dp2), Der p 10 (Dp10) and Dp23 IgE were determined in serum samples from 532 patients with HDM allergic asthma and allergic rhinitis in the MITRA trial (Virchow, JAMA 2016). Dp1, Dp2 and Dp23 IgG4 were measured in serum samples from the same subjects at baseline and end of trial. All antibody measurements were analysed by ImmunoCap (Thermo-Fisher). The allergen content of the SQ HDM SLIT-tablet was analysed by mass spectroscopy (MS). Statistical analyses were performed with SAS JMP version 14.1.0.
Results: While sensitisation frequencies of Dp1, Dp2 and Dp23 were 78%, 86% and 66%, respectively, only 5% of the subjects were sensitised towards the minor allergen Dp10. At baseline, the majority (92%) of the subjects were sensitised towards Dp1 and/or Dp2 and only a marginally higher fraction (94%) of the population was identified by including Dp23 sensitisation as an additional parameter in the analysis. In contrast to the high sensitisation frequency the mean concentration of Dp23-specific IgE (2.6 kUA/L) was low compared to Dp1 (7.9 kUA/L) and Dp2 (10.8 kUA/L), and at the level of IgE towards the minor allergen Dp10 (3.4 kUA/L).
MS analyses demonstrate the presence of Dp23 in the SQ HDM SLIT-tablet which was reflected in the SLIT-induced immune response. Similar to Dp1 and Dp2, subjects with Dp23 IgE at baseline showed a statistically significant increase in Dp23-specific IgG4 at the end of trial. In order to assess the clinical relevance of Dp23 sensitisation subjects were stratified with regard to their baseline Dp23 sensitisation status. In this sub-group analysis, the Dp23 sensitisation status did not seem to influence clinical outcomes of HDM SLIT such as the odds-ratio for asthma exacerbations or the probability of experiencing the first asthma exacerbation during treatment.
Conclusion: While the SQ HDM SLIT-tablet contains immunologically relevant amounts of all 3 major allergens, the diagnostic value of Dp23 IgE is minimal and stratification based on Dp23 does not appear clinically relevant.

OA0106 | Altered chromatin landscape in T follicular cells in seasonal allergic rhinitis and following allergen-specific immunotherapy

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Background: Allergen-specific immunotherapy (AIT) administered either subcutaneously (SCIT) or sublingually (SLIT) has been

shown to induce long-term T cell tolerance to the sensitising allergen. However, the mechanism has yet to be fully elucidated. We hypothesised that circulating $CD4^+CXCR5^+PD\text{-}1^+$ T follicular helper (Tfh) and $FoxP3^+$ T follicular regulatory (Tfr) cells are dysregulated in patients with seasonal allergic rhinitis (SAR) and are restored following AIT. Moreover, these changes are underscored by changes in the cellular chromatin landscape in Tfh and Tfr cells.

Method: In a cross-sectional study of allergen-specific immunotherapy, PBMCs were isolated from non-atopic (NA, n = 13), SAR (n = 13), SCIT (n = 10) and SLIT (n = 8) groups. Circulating Tfh and Tfr cells were enumerated by flow cytometry. Cellular chromatin accessibility was assessed by ATAC-seq.

Results: $ICOS^+$ Tfh cells, $IL\text{-}4^+$ Tfh cells, $IL\text{-}21^+$ Tfh cells and dual $IL\text{-}4^+IL\text{-}21^+$ Tfh cells were higher in SAR compared to NA, SCIT and SLIT (all, $P < .05$). In contrast, $FoxP3^+$ Tfr cells and $CTLA\text{-}4^+$ Tfr cells were dysregulated in SAR and were restored in SCIT ($P < .05$) and SLIT ($P < .05$) groups. ATAC-seq analyses showed that there was a significant change in chromatin accessibility in genes such as *STAT4* that drives IL-21 production in Tfh cells compared to Tfr cells in NA. In contrast, regulatory gene such as *FOXP3* that encodes for FoxP3 was more accessible in Tfr cells compared to Tfh cells in NA. Furthermore, there was a trend of higher chromatin accessibility of *IL4* and *IL21* genes in Tfh cells in SAR compared to NA. Genes encoding regulatory proteins, such as *IKZF2*, *TNFRSF18*, *PRDM1*, *IL10RA* and *IFNG* (encodes for Helios, GITR, Blimp-1, IL-10 receptor and IFN-γ, respectively) showed evidence of higher chromatin accessibility in SCIT compared to SAR. In addition, genes encoding GITR, *TNFRSF18* also showed higher chromatin accessibility in SLIT compared to SAR.

Conclusion: For the first time, we showed a dysregulation of Tfh cells and Tfr cells in SAR. Allergen-specific immunotherapy induces "protective" regulatory cells, which was underscored by changes in the chromatin landscape, suggestive of epigenetics modification.

OA0107 | The FAB-assay—useful tool for evaluating successful immunotherapy or reflection of specific-IgG4?

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Background: The facilitated antigen binding (FAB)-assay is discussed as one potential biomarker for monitoring successful allergen immunotherapy (AIT). Here, the aim was to evaluate, if the assay is suitable to determine treatment success on single patient basis in birch and grass pollen IT by correlating the treatment received, the clinical data, the FAB-assay results, and specific-(s) IgG_4.

Method: The FAB-assay with grass and birch pollen extract (GPE, BPE) was performed blinded with 57 sera of a double-blind randomized multicenter clinical trial. Included were patients with dual allergy (birch and grass) that were either treated with grass (n = 30) or birch (n = 27) pollen allergoid (PA), one group served as the control for the other group. Effects of AIT were assessed by measuring nasal symptoms upon grass and birch pollen exposure in an environmental challenge chamber (ECC) with each allergen before and after 9 months of AIT. Furthermore, $sIgG_4$-values were determined.

Results: Correlating FAB-assay- and ECC-results revealed congruence (i.e. identical results for responder and non-responder with both methods) of up to 74% (BPA-treated) and of 53% (GPA-treated), respectively. This outcome was mainly due to the effect that patients treated with grassPA showed also an improvement of symptoms upon birch pollen-exposure in the ECC, and vice versa. This effect was not detectable by the FAB-assay. If the assay should have detected these patients or not needs to be specified, since it was not possible to determine, if the described ECC-finding is unspecific (= false-positive) or a bystander (=true-positive?) effect.

Analyses of $sIgG_4$-data showed that all patients undergoing AIT had increased levels of $sIgG_4$ with the respective IT-allergen. In both treatment groups, some patients could be identified that display high $sIgG_4$-levels although they did not receive AIT with the corresponding allergen. Interestingly, those patients were FAB-assay-non-reactive.

Conclusion: Generally, it is still under discussion whether or not a good biomarker should give identical results compared to the clinical data, especially, because the main requirement for biomarker is superiority to subjective (symptom) measurements. However, since correlation of the FAB-assay with the treatment received was overall good and furthermore, the FAB-assay is no pure reflection of $sIgG_4$-levels, the assay is still an interesting candidate-biomarker for AIT.

MONDAY, 3 JUNE 2019
OAS 19
AVENUES IN IMMUNOMODULATION

OA0109 | Immunomodulatory effects of adipose stem cells-derived extracellular vesicles on Th2-mediated inflammation in lung epithelial cells

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Background: Although stem cell-derived extracellular vesicles (EVs) have been shown to facilitate regeneration of injured tissue, there is no report that evaluates the immune-modulating effect of stem cell-derived EVs on Th2-mediated inflammation. We evaluated the immunomodulatory effects of adipose stem cells (ASCs)-derived EVs on Th2-mediated inflammation induced by *Aspergillus* protease antigen in lung epithelial cells.

Method: The EVs were isolated from supernatant of ASCs and images were obtained by transmission electron microscopy. The diameters of EVs were measured by using dynamic light scattering. The primary lung epithelial cells and mouse lung epithelial cells were pre-treated with 200 ng/ml of *Aspergillus* protease for 2 hours, and then treated with 10 μg/50 μl of ASC-derived EVs. Real-time PCR was performed to determine the levels of eotaxin, IL-25, TGF-β, and IL-10 after EV treatment. To evaluate the role of EVs in macrophage polarization and dendritic cells (DCs) differentiation, *in vitro* bone marrow-derived macrophage and DCs stimulation assay was performed.

Results: The average quantity and size of ASCs-derived EVs was 3.850 mg/ml and 130.3 ± 65.7 nm, respectively. The gene expression of eotaxin and IL-25 was significantly increased after *Aspergillus* protease stimulation. However, EV treatment significantly decreased the expression of eotaxin and IL-25 in both lung epithelial cells. The expression of TGF-β and IL-10 were significantly increased after EV treatment. EV treatment significantly increased the gene expression of M2 macrophage marker such as Arg1, CCL22, IL-10, and TGF-β. Furthermore, EV treatment significantly increased the expression of co-stimulatory molecules such as CD40, CD80, and CD 86 in immature DCs.

Conclusion: EVs of ASCs have immunomodulatory effects on Th2-mediated inflammation induced by *Aspergillus* protease antigen, characterized by down-regulation of eotaxin and IL-25, and up-regulation of TGF-β and IL-10.

OA0110 | The cannabinoid receptor agonist WIN55,212-2 impairs peanut-induced allergic features by promoting the generation of tolerogenic dendritic cells

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Background: Different mouse models have established that the endocannabinoid receptors (CB1 and CB2) modulate allergic responses. We showed higher expression levels of CB1 in peripheral blood mononuclear cells and tonsils of allergic patients than in healthy donors. Human dendritic cells (DCs) express CB1 and CB2, but their actual role in allergy and the underlying immunological mechanisms remains unknown. Here, we employed the cannabinoid receptor agonist WIN55,212-2 to investigate the role of cannabinoid receptors signaling on DC activation in the context of peanut allergy, and their potential as therapeutic target for treatment of allergic diseases.

Method: To ascertain the impact of WIN55,212-2 on DC activation, human monocyte-derived DCs (hmoDCs) were stimulated with peanut and/or WIN55,212-2, and functional changes were assayed in allogenic co-cultures with naïve $CD4^+$T cells. Cell surface markers and cytokines were quantified by flow cytometry and ELISA, respectively. To examine the effects of WIN55,212-2 *in vivo*, Balb/c mice were subjected to epicutaneous sensitization to peanut for 3 consecutive days in the absence or presence of WIN55,212-2. DC activation and migration into the draining lymph node was assessed by total cell counts and cytometric analysis. A mouse model of peanut-induced anaphylaxis was also developed to assess the potential therapeutic effects of WIN55,212-2.

Results: HmoDCs express CB1 and CB2. WIN55,212-2 down-regulated peanut-induced DC activation as per lower expression of HLA-DR, CD86 and CD83, as well as IL-6 secretion without affecting cell viability. WIN55,212-2 generated, in the presence of peanut, tolerogenic hmoDCs that induced a higher frequency of $CD4^+CD25^+CD127^-FOXP3^+$ regulatory T cells, and IL-10 production, as compared to peanut-stimulated DCs alone. WIN-treated mice exhibited a lower number of activated DCs in the draining lymph node as compared to peanut-sensitized mice, which presumably impaired humoral responses and clinical reactivity on challenge.

Conclusion: The cannabinoid agonist WIN55,212-2 endorses functional tolerogenic DCs under conditions that are prone to Th2 immunity. The ability of WIN55,212-2 to potentiate the DC-T regulatory cell axis could be exploited for the development of novel therapeutic strategies in allergy and other immune-tolerance related diseases.

OA0111 | PP-001, A new small molecule for intraocular treatment of uveitis—preclinical data and first results of a prospective multicenter clinical trial

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Background: Experimental autoimmune uveitis (EAU) in rats as a suitable model for the respective intraocular inflammatory disease in humans was used to investigate the effect of the new small molecule dihydroorotate dehydrogenase inhibitor PP-001. After successful systemic application in our rat model, we investigated intraocular injection in relapsing EAU as well as in uveitis patients (clinical phase I trial).

Method: Relapsing EAU was induced in Lewis rats by immunization with retinal autoantigen peptide R14. After resolution of the first attack of EAU PP-001 or saline was injected intravitreally and the eyes observed for further relapses of uveitis. PP-001-treated, R14-specific rat T cells lines and human PHA-stimulated lymphocytes were investigated for proliferation and cytokine secretion. In a prospective, multicenter clinical phase-1 study three groups of patients (n = 4) received a single dose of 300, 600 or 1200 ng intravitreal PP-001. All patients maintained their systemic medication during the study. The main outcome measures were ocular and systemic safety, pharmacokinetics in peripheral blood and efficacy.

Results: Intraocular injection of PP-001 after resolution of R14-induced rat EAU significantly suppressed the number and intensity of relapses for 6 days. Proliferation of autoantigen-specific rat T-cell lines and secretion of IFN-γ, IL-17, IL-10, IP-10 and VEGF were efficiently suppressed by PP-001. PP-001 also suppressed proliferation and cytokine secretion of PHA-stimulated human PBL without affecting the viability of the cells. PP-001 showed no toxic effect on rat eye tissues after intraocular injection. The clinical trial revealed no major systemic or ocular side effects. Minor side effects were related to the injection procedure but not to the study drug, which was well tolerated. Compared to baseline visual acuity was increased in the treated eyes of all study groups 14 and 28 days after injection; the fastest and highest increase of average 15 letters was observed in the 1200 ng group until the last follow-up at day 28.

Conclusion: Here we present a novel drug for systemic and local treatment of autoimmune uveitis without adverse effects on resident ocular cells. In patients with noninfectious uveitis intravitreal PP-001 can improve vision and is safe and well tolerated without adverse side effects. The therapeutic effect lasts up to 4 weeks. Sustained release formulations are under investigation for prolonged efficacy.

OA0112 | STAT3 gene suppression as an approach for the treatment of non-eosinophilic bronchial asthma

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Background: The pathogenesis of nonallergic bronchial asthma (BA) is connected with Th17-cell proliferation and neutrophilic airway inflammation. STAT3 is a crucial for Th17-cell polarization. The aim of this study was to assess the activity of the complex consisting of the carrier peptide b-LTP and siRNA molecules targeted to STAT3 gene in a mouse model of neutrophilic BA.

Method: Female BALB/c mice were divided into 4 groups. Groups 1–3 were i.p. sensitized on days 0, 14, 28 with the mixture of 20 μg ovalbumin (OVA) and 100 μl Freund's adjuvant (FA). On days 41-43 mice were inhaled for 20 min with the mixture of 10 mg/ml OVA and 0.4 mg/ml LPS from *E. coli*. Group 4 was intact mice. 2 hours before inhalation with OVA/LPS mixture mice from group 3 were nebulized with siSTAT3/b-LTP complex at conc. 1.1 mg/ml. Similarly, group 2 received siGFP/b-LTP complex consisted of non-specific siRNA against GFP gene. On day 44, bronchial hyperreactivity (BHR) was measured by non-invasive plethysmography. Blood was sampled for ELISA to assess the levels of antibodies. On day 45 bronchoalveolar lavage (BAL) was collected for differential cell count. Gene expression in BAL cells was determined by real-time PCR.

Results: Mice received siSTAT3/b-LTP complex demonstrated the decrease in STAT3 gene expression by 20%, compared to animals inhaled to siGFP/b-LTP, that led to downregulation of IL-17F and IL-17A genes expression by 40% and 35%, respectively. Groups 1-3 showed elevated levels of allergen-specific IgE, IgG1 and IgG2a antibodies; there was an increase in the level of IgG2a by 40% after suppression of STAT3. BHR was 20% elevated in all groups compared to control; there were no changes in BHR after STAT3 suppression. BAL analysis showed a pronounced infiltration of neutrophils into the lungs of groups 1 and 2 (39800 ± 6591 and 81832 ± 5330 cells/ml, respectively). Downregulation of IL-17F and IL-17A genes led to 3.2-fold significant decrease in the number of neutrophils (to 25389 ± 3696 cells/ml) compared to group 2. the number of neutrophils in group 4 did not exceed 1000 cells/ml. Histological analysis of lung tissue in general confirmed these data.

Conclusion: Inhalation of the complex consisted of peptide carrier b-LTP and siRNA targeted to STAT3 gene leads to substantial decrease neutrophil-mediated inflammation in the lungs. It could be a promising approach to treat neutrophilic asthma.

OA0113 | Identification of nut lipid-specific NKT receptors and their role on the intrinsic allergenicity of nut proteins

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Background: We have previously shown that lipids are required for some proteins to act as allergens. Lipids and non-peptide ligands are presented by Antigen presenting cells (APCs), via MHC-like molecules (CD1), and activate unconventional T cells (NKT, LC and others). Natural Killer T cells (NKT), a sub-class of unconventional T-cells, bind via T cell receptors (TCRs) complex lipid antigens presented by CD1 at APCs and when activated, secrete specific cytokines.

Method: In the search for lipid receptors involved on the intrinsic allergenicity of nut proteins, we are using stable human T-cell line (Jurkat with a luciferase reporter gene) to express recombinant lipid-binding TCRs. Here we will show preliminary work on: i) the optimisation of the co-culture parameters required to improve the internal signal of the reporter construct; ii) the optimisation of the markers for activated human NKT cells, using FACS analysis; iii) the isolation and identification of lipid-binding NKT cells from primary human culture with the aim of characterizing lipid-binding TCR sequences.

Results: The preliminary results have shown that a murine NKT cell hybridoma line can be transfected to express a human lipid-binding TCR. The percentage of labelled TCR Jurkat Lucia cells expressing human TRAV10/TRBV25 protein receptors has increased for over 72 hours. Initial characterization of different activation NKT cell markers has shown that CD69 was the most suitable activation marker for activated NKT primary cells. NKTs successfully isolated from PBMCs from six volunteers (4 allergic and 2 healthy) resulted in over 200 TCR sequences.

Conclusion: Three pair of nut lipid-specific TCR sequences were identified and are currently been assembled and tested into the in vitro cell system. Future work will involve screening of natural nut lipids. Our preliminary results suggest that natural plant lipid and NKT cells might be involved into the intrinsic allergenicity of nut proteins.

MONDAY, 3 JUNE 2019
OAS 20
PATHOPHYSIOLOGY AND DIAGNOSIS OF ALLERGIC RHINITIS

OA0114 | Association of the CD14 (-159C/T) SNP with house dust mites sensitization in patients with perennial allergic rhinitis in the population of ukraine

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Background: Previous studies have shown that the single nucleotide polymorphism detected at position −159 in the promoter region of the *CD14* gene (rs2569190) is associated with asthma and allergic rhinitis in various ethnic populations.

Method: There were studied CD14 rs2569190 polymorphism of CD14 receptor gene in 93 patients with perennial allergic rhinitis. The control group included 90 non-atopic volunteers. SNP of -159C/T was detected by allele-specific PCR. Allergy sensitization was confirmed by skin prick tests. Patients and volunteers were recruited at the Bogomolets National Medical University, Kyiv, Ukraine and provided written informed consent for the genetic study.

Results: In the control group, the frequency distribution of genotypes (C–20 (22.2%), CT–48 (53.3%), TT–22 (24.5%)) was significantly different from perennial allergic rhinitis (CC–40 (43.0%), CT–35 (37.6%), TT–18 (19.4%), $\chi 2 = 6.20$, $P = .013$) phenotypes. The risk analysis for the T allele ([CC]<->[CT+TT]) showed that the frequency of the genotype CT+TT in patients with perennial allergic rhinitis (57.0%) was significantly lower (OR = 0.379, CI=[0.199-0.721], $\chi 2 = 8.97$, $P = .003$) compare to control group (77.8%). Distribution between genotypes and sensitization to allergens—House Dust Mites: CC—28, CT—20, TT—9; Cat: CC—7, CT—10, TT—3; Dog: CC—5, CT—5, TT -6. There is an increased risk of perennial allergic rhinitis in the general group and in the subgroup with House Dust Mites sensitization, but not in patients with sensitization to cat and dog allergens.

Conclusion: The CD14 (-159C/T) SNP is associated with House Dust Mites sensitization in Patients with perennial allergic rhinitis in the population of Ukraine

OA0115 | Replication study of susceptibility variants associated with allergic rhinitis and allergy

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Background: Allergic rhinitis (AR) is believed to be complex genetic diseases resulting from the effect of both multiple genetic and interacting environmental factors on their pathophysiology. The last decade has been marked by the publication of more than 20 genome-wide association studies (GWASs) of AR and associated allergic phenotypes and allergic diseases have been shown to share a large number of genetic susceptibility loci, although few of these have been convincingly replicated especially in Chinese. The aim of present study is to investigate the highly replicated allergy-related genes and variants as candidates for AR in Han Chinese.

Method: A total of 762 AR patients had a history of AR for at least 1 year and fulfilled all AR criteria of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines and 760 health controls were recruited. All subjects were of Han Chinese ethnic origin from the Beijing region, China. The study protocol was approved by the Ethics Committee of Beijing TongRen Hospital and each individual provided written informed consent prior to entry in the study. 55 susceptible single nucleotide polymorphisms (SNPs) previously reported as associated with allergic traits were choose for replication. SNPs were typed using iPLEX chemistry on a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer.

Results: The allele frequencies of rs9865818 in LIM Domain Containing Preferred Translocation Partner In Lipoma (LPP), rs6554809 in Dynein Axonemal Heavy Chain 5 (DNAH5) and rs1438673 in Thymic Stromal Lymphopoietin (TSLP) were significantly different between the cases and controls: rs9865818: A>G, rs6554809: C>T ($P = .007$), rs1438673: T>C ($P = .014$), and they remain associated after 100,000 permutations ($P < .05$). In the single-locus analyses, logistic regression analyses revealed that in the codominant-effect model as assessed by the Akaike's information criteria (AIC), compared with wild-type carriers, significant AR risk was associated with LPP SNP rs9865818, DNAH5 SNP rs6554809, rs1438673, rs7775228 and rs7203459.

Conclusion: LPP, DNAH5 and TSLP were also plausible candidates in terms of their biological function in the development of AR.

OA0116 | Severe respiratory allergic patients undergo oral mucosa remodelling prior to food allergy

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Background: In a previous study, we demonstrated that severe grass pollen allergic patients that suffer profilin-mediated food allergy undergo oral mucosa remodelling. This suggests that oral mucosa may be key in the progression of respiratory to food allergic reactions. However, oral mucosa features in allergic inflammation remain largely unexplored. In this study, we aim to investigate whether oral remodelling occurs in severe respiratory allergic patients in the absence of food allergy, and independently of the allergen involved.

Method: To test these hypotheses, we recruited two groups of patients: patients with positive Skin Prick Test (SPT) to olive allergens Ole e1 and Ole e7 and severe allergic reactions, and patients allergic to house dust mites who experienced anaphylaxis when eating mite-contaminated flours. We studied oral mucosal features by histological and immunohistochemical analyses in biopsies taken from the cheek lining of these patients and compared with a control group of non-allergic subjects.

Results: We observed a significant decrease in epithelial protein expression of the junctional complexes and increased collagen deposition in both groups of severe allergic patients. Although we could not find major differences in angiogenesis or immune cell counts, differential expression of FcεRI and an increased Treg population was observed in allergic patients. Eosinophils and neutrophils were hardly present in the oral mucosa of any study subjects.

Conclusion: Severe respiratory allergy causes oral mucosa remodelling independently of food allergy and the allergen involved. Besides, this remodelling occurs in the absence of inflammatory infiltrate recruitment. These findings highlight the need to understand how systemic inflammatory mediators affect mucosal integrity.

OA0118 | Perennial allergy induces eosinophilia in polyps but not in nasal mucosa

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Background: Nasal polyps (NP) are peduncular tissue that arises from nasal sinuses to the nasal cavity, product of maintained inflammation. NP are strongly associated with local type 2 inflammatory response with eosinophil infiltrates, thus allergy has traditionally been considered as a major cause of NP development. However, studies are inconclusive, and allergy role in NP remains unknown. Here, we classify patients with NP according to their allergic phenotype in order to better understand the role of allergy in the onset and progression of nasal polyposis.

Method: Twenty-seven adult patients were recruited for this study. Plasma samples were obtained and *in vitro* screening of specific IgE against aeroallergens (ImmunoCAP®-ISAC) or *S. aureus* enterotoxins A & B (ImmunoCAP®) was performed. Metabolomic analysis was done by LC-MS, and significant analytes identified through MS/MS fragmentation. Both polyp and non-polyp nasal mucosa biopsies were obtained from participants, and a local analysis of eosinophilia, goblet cell hyperplasia and remodeling features was done by means of Luna, PAS, and H&E stains and immunohistochemistry with claudin-1 antibody, respectively.

Results: Patients were classified, according to allergic phenotype, in non-allergic (48.2%), seasonal allergic (18.5%) and perennial allergic (33.3%) patients, which represents an increase in allergy incidence (51.8%) compared to average population. Higher levels of eosinophilia were found in polyp tissue compared to non-polyp tissue ($P < .001$), especially in perennial-allergic patients, showing significant differences between their polyps and non-allergic patients' polyps ($P < .05$). Goblet cells were increased in NP compared to nasal mucosa tissue ($P < .05$) independently of allergic phenotype. Allergic patients showed thickened epithelium of the nasal mucosa compared to non-allergic patients ($P < .05$), but no differences were found in tight-junction integrity, evaluated by claudin-1 distribution and quantification. Metabolomic study spotted fifteen compounds comprising lysophospholipids, fatty acids and retinol. Most of them were decreased in perennial allergic patients.

Conclusion: Prevalence of allergy is augmented among patients with NP, and patients with NP and allergy have distinctive features, such as eosinophilia in NP but not in nasal mucosa, epithelial acanthosis in mucosa and a differential metabolic finger print. Therefore, determining the specific allergic phenotype can be useful for a better management of the disease.

OA0119 | A combination corticosteroid and antihistamine targets key innate immune pathways at the nasal mucosa in allergic rhinitis

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Background: A novel formulation of azelastine hydrochloride and fluticasone propionate in a single spray has been shown to provide greater symptom relief than treatment with either compound alone in individuals with moderate / severe allergic rhinitis. The aim of this study was to characterise the effect of either intra-nasal azelastine (Azep), fluticasone propionate (Flixonase) or a combination formula of azelastine hydrochloride and fluticasone propionate in a single

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spray on mucosal immune gene expression in the nose of individuals with moderate to severe AR.

Method: This was a double-blind, three-armed parallel group study in which 48 individuals (n = 16 per group) with moderate/severe AR and sensitive to dust-mite only or dust mite and grass allergens completed a 14-day medication washout followed by a seven-day treatment period. Participants completed a symptom and medication diary and the mini-rhinoconjunctivitis quality of life (m-RQLQ) questionnaire daily. At day 0 (pre-treatment) and day 7 (end of treatment) participants completed the visual analogue scale (VAS) and provided a nasal lavage and blood sample. Samples were analysed with the PanCancer Immune Profiling kit (Nanostring Technologies, Seattle, USA).

Results: All clinical and laboratory baseline parameters were similar in the groups with the exception of a significant difference in eosinophil counts, with the Azep group having a 50% lower eosinophil count than the Flixonase group (P = .04) but not the Dymista group. Participants in the Dymista group had the strongest statistically significant reduction in symptoms and improvement in quality of life (P < .0001). A total of 588 immune genes were expressed above background thresholds in nasal lavage samples across the three groups. Flixonase altered the expression of 148 genes significantly, compared to 56 immune genes in the Dymista group and 23 immune genes in the Azep group. Gene set analysis indicates that Flixonase altered the greatest number of pathways (n = 142 Flixonase; n = 53 for Dymista; n = 37 for Azep). Dymista significantly altered a number of innate immune pathways that were not altered by the monotherapies.

Conclusion: The observation that Dymista alters innate immune pathways provides insight into potential mechanisms to explain the clinical effects observed with this combination therapy and provides potential biomarkers to target in other atopic conditions.

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TREATMENT OF FOOD ALLERGY

OA0120 | Extended daily dosing of AR101 for peanut allergy results in higher tolerated doses and continued immunomodulation

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Background: In PALISADE, a phase 3 study of AR101, immunological changes suggested immunomodulation of peanut allergy during the 1st year of active treatment, including 6 months maintenance. We report on subjects' ability to tolerate doses of > 1000 mg peanut protein during a double-blind, placebo-controlled food challenge (DBPCFC); safety; and immunological changes after an additional 6 months of daily extended maintenance (EM) therapy.

Method: PALISADE completers were eligible to enter the follow-on study. A subset of subjects continued 300 mg AR101 daily EM, after which a DBPCFC, including an additional 2000 mg (4042 mg cumulative) challenge dose, was undertaken. Peanut skin prick test (SPT) and peanut-specific IgE (psIgE) measurements at the end of the EM period were compared to those at PALISADE exit. Medians (Q1, Q3) are reported for efficacy and immune measures.

Results: 269/314 (86%) AR101-treated subjects rolled into the extension study; 117 (37%) were assigned to the daily EM regimen, the focus of this analysis. 109 (93%) subjects completed the DBPCFC after 6-month EM. Adverse events (AEs), regardless of causality, were similar during both periods (PALISADE 86% vs EM 83%). 4 subjects (3%) discontinued during EM due to AEs: 3 were treatment-related (1 eosinophilic oesophagitis, 2 systemic allergic reactions). After the 6 months of AR101 EM, median tolerated dose was 1000 mg (1000, 2000). Of subjects who tolerated < 1000 mg at PALISADE exit (n = 39), 69% (n = 27) tolerated a higher challenge dose after EM, increasing from 600 mg (300, 600) to 1000 mg (1000, 2000). 49% of subjects tolerated the highest 2000 mg challenge dose (4043 mg cumulative). Immunological changes continued during EM (PALISADE exit vs EM; all comparisons, $P < .001$), including SPT wheal diameter (7.5 mm [6.0, 10.0] vs 7.0 mm [5.0, 9.0]); psIgE (58.0 [19.8, 225.3] vs 38.5 [14.4, 97.4]); and psIgE/IgG4 (11.2 [2.7, 29.9] vs 5.5 [1.1, 14.9]).

Conclusion: AR101 was well tolerated after an additional 6 months of daily EM (300 mg) therapy, with similar AE profiles reported during both maintenance periods. 86 (79%) participants could tolerate a 1000 mg challenge dose. Of those, 53 (49%) tolerated the highest 2000 mg challenge dose (4043 mg cumulative). The clinical findings of higher tolerated doses were matched by favourable immunological changes, suggestive of ongoing immunomodulation during the additional daily dosing maintenance period, reinforcing the rationale for continued daily AR101 dosing after 1 year.

OA0121 | High rate of sustained unresponsiveness in peanut-allergic children undergoing oral immunotherapy using heat-modified peanut: Results from the BOPI study

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Background: Peanut oral immunotherapy (OIT) is clinically efficacious but desensitisation is usually dependent on ongoing maintenance treatment, with typically around one third of treated subjects maintaining desensitisation after stopping treatment. We evaluated the rate of sustained unresponsiveness in children undergoing OIT using heat-modified peanut to induce desensitisation in the BOPI study, a Phase 2b/3 randomized controlled trial.

Method: Children with peanut allergy confirmed at double-blind, placebo-controlled food challenge (DBPCFC) underwent oral immunotherapy (updosing using boiled peanut for ~6 months, followed by maintenance with roasted peanut). Participants underwent repeat DBPCFC at 12 months to assess response, following which peanut was stopped and sustained unresponsiveness assessed after 4 weeks off treatment (4-SU). Clinicaltrials.gov NCT02149719.

Results: Forty-seven children (8-17 years, 43% female) were enrolled. Baseline serum-specific IgE to peanut was 35.8 (IQR 5.1 to > 154) kUA/l, and 7.4 (IQR 2.4-75) kUAl to Ara h 2. Median cumulative eliciting dose prior to OIT was 143 m peanut protein (IQR 43-443 mg); 11 (23%) had anaphylaxis (lower respiratory symptoms) at baseline challenge. Thirty-eight completed 12 months of OIT, all of whom achieved the primary outcome of desensitisation to > 1.4 g peanut protein ($P < .0001$); 25 tolerated > 4.4 g peanut protein. 22 participants (47% by ITT, 58% per protocol) achieved 4-SU.

Conclusion: Oral immunotherapy using boiled peanut is pragmatic and effective, with a high level of sustained unresponsiveness at 4 weeks after 1 year of treatment.

OA0123 | Identifying allergic children with severe adverse events during oral peanut challenges in the LEAP studies by assessing basophil activation

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Background: Oral food challenge (OFC) is the gold-standard to diagnose peanut allergy (PA) and to confirm eligibility for and assess response to treatments for PA; however, OFCs involve a significant risk of allergic reactions of unpredictable severity. The LEAP and associated cohorts presented a unique opportunity of assessing the basophil activation test (BAT) as a biomarker of peanut allergic reactions.

Method: Participants in the LEAP (n = 474), LEAP-On (n = 423, the follow-up study of LEAP) and PAS (n = 84) studies underwent BAT, skin prick test, specific IgE (sIgE) and IgG4 to peanut and sIgE to Ara h 1, 2, 3, 8 and 9. BAT results were analyzed in relation to the LEAP study intervention, PA status (applying the previously defined cut-off of ≥ 4.78% CD63 + basophils), severity and threshold of allergic reactions at OFC to peanut, and were compared with the results of the other biomarkers.

Results: In the LEAP study, peanut consumers had lower proportion of activated basophils following peanut stimulation compared to peanut avoiders ($P < .001$) and this effect was sustained after 1 year of peanut avoidance in the LEAP-On study. BAT diagnosed PA with high specificity (97.6%) and was inversely correlated with IgG4/IgE ratios (Pearson correlation = −0.64, $P < .001$). Participants reacting to lower doses of peanut protein at OFC had both higher proportion of activated basophils and higher basophil sensitivity, as measured by CD-sens (Spearman's rho = −0.3, $P < .001$). Participants with severe/life-threatening peanut reactions during OFC had higher proportion of activated basophils to peanut compared to participants with mild/moderate reactions ($P < .001$). BAT identified severe reactors with 100% sensitivity and 95% specificity, with larger area under the ROC curve (0.985) compared with the other biomarkers. Nomograms to calculate the probability of serious adverse events during OFC for individual patients in the specialist setting (using SPT, Ara h 2-sIgE and BAT) and in the generalist setting (using SPT and peanut-sIgE) were generated and internally and externally validated in a distinct cohort (n = 88), showing consistency and reproducibility.

Conclusion: LEAP peanut consumers had lower basophil activation to peanut than peanut avoiders and this effect was sustained after 1 year of peanut avoidance. BAT diagnosed PA with high specificity and identified severe reactors with high specificity and high sensitivity. Nomograms can help estimate the likelihood of severe reactions in individual peanut allergic patients.

OA0124 | The novel long-acting IgETrap-Fc fusion protein GI301 elicits therapeutic synergy in combination with probiotics for the treatment of food allergy

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Background: Food allergy is a common and potentially fatal condition that has dramatically increased in incidence over the last decade. Although the efficacy of oral desensitization immunotherapy (OIT) for food allergy has been demonstrated to some extent, adjunctive approaches with anti-IgE therapy and probiotics might improve outcomes for OIT patients. Observations suggest that OIT in combination with omalizumab may enhance desensitization to food allergens more quickly and safely than OIT alone. However, the use of omalizumab is associated with anaphylaxis and is not approved for patients under 12 years of age with chronic spontaneous urticaria or those under 6 years of age with uncontrolled asthma.

Method: GI301 is a novel long-acting IgE_{Trap}-Fc fusion protein comprising the human FcεRI extracellular domain fused to a human IgD/IgG4 hybrid Fc region lacking binding sites for IgG receptors and C1q. Affinity for IgE was determined by SPR assay and the capacity to inhibit mast cell degranulation was examined using bone marrow-derived mast cells from transgenic mice expressing human IgE and FcεRI. The therapeutic effects of GI301 in combination *B. longum* were evaluated using an ovalbumin-induced murine food allergy model.

Results: GI301 has more durable binding to human IgE with 70-fold higher affinity (Kd: 2.2×10^{-10} vs. 1.5×10^{-8}) and elicits 59-fold more potent inhibition of mast cell degranulation (IC_{50}: 11 ng/mL vs. 650 ng/mL) than omalizumab. While omalizumab's high affinity to IgG receptors may potentiate IgG-mediated anaphylaxis, GI301 does not bind Fcγ receptors. We previously demonstrated that *B. longum* induces mast cell apoptosis without affecting free IgE levels. GI301 in combination with *B. longum* alleviates food allergy symptoms to a greater extent than GI301 or *B. longum* alone, in association with profound reductions in free IgE and IL-33 mRNA levels, as well as mast and goblet cell numbers in the small intestine of food allergy-induced mice.

Conclusion: GI301 is superior to omalizumab in binding free IgE and is a more potent inhibitor of mast cell degranulation. The therapeutic synergy of GI301 in combination with *B. longum* observed in-vivo indicates that the combinational approach may address the significant unmet needs remaining for food allergy patients.

OA0125 | Post desensitization strategy after successful oral immunotherapy to egg

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Background: Recent studies, meta-analysis, guidelines, suggest that oral immunotherapy (OIT) offers an effective modality for the active management of many children with IgE mediated food allergy. Currently is unclear which is the best maintenance dietary regimen after desensitization is achieved. In this randomized , controlled study we evaluated the post –desensitization effectiveness, in children allergic to egg, defined as the ability after OIT to consume hen's egg (HE) no more than two times per week along with a free diet.

Method: After successfully terminating desensitization to HE, patients were randomly allocated to two groups. Group A was prescribed a regimen involving the ingestion of half an egg for five times per week. Group B received a maintenance regimen involving the ingestion of half an egg two times per week. Free diet included foods containing HE proteins such as: biscuits, cakes, desserts, ice creams, pasta. The approximate weight of half an egg is 10 grams. To avoid prolonged burden for patients i.e. "ad libutum diet", the study lasted 3 months.

Results: Forty –eight subjects (21 males , age range 4-15 years) where therefore randomized 24 in Group A and 24 in Group B. Forty-six completed the study: 22 in Group A and 24 in Group B. Among patients of both groups the appearance of adverse vents was quite uncommon. Two episodes of abdominal pain an one of rhinitis was reported by three patients of Group A. In Group B, four patients reported abdominal pain an one patent generalized Urticaria. No statistical difference was observed (P = .08) None of participants discontinued permanently the maintenance diet due to the appearance of adverse events. In addition, no difference had been observed in two groups concerning decrease of HE specific IgE (KU/L) P = .07. Increase of specific IgG4 (mcg/ml) P = .09. Wheal diameter HE—SPT (mm/median range) P = .07.

Conclusion: So far there are only sparse data concerning the fact that patients deserve an adequate post-desensitisation strategy after successful desensitization to food(s). In present study, we explored the possibility to simplify the dietary regimen after HE–OIT. According to the data obtained a maintenance of egg twice weekly is as effective and safe as the frequent "ad libitum " administration is. In addition, immunologic parameters (e.g. specific Ig response) show no significant difference between the two regimens.

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IMMUNOPATHOGENESIS OF PEDIATRIC ALLERGIC DISEASES

OA0126 | Breast milk fatty acid composition of allergic and non-allergic mothers: The ulm SPATZ health study

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Background: Human milk is considered the most suitable form of nourishment for all infants including those with allergies. There is a growing interest in the question whether breast milk (BM) of allergic mothers is different from BM of non-allergic mothers. Most previous studies have compared BM fatty acid (FA) composition of small sub-groups and did not account for existing correlations within compositional data. We aimed at determining differences in BM FA composition in relation to maternal allergy within a large birth cohort study using appropriate statistical methods accounting for these correlations.

Method: Breast milk samples were obtained from breastfeeding mothers at 6 weeks (n = 587), 6 months (n = 482) and 12 months (n = 81). Demographic information and maternal history of allergic disease (hay fever, asthma or atopic dermatitis) were collected using a self-administered questionnaire. FAs were measured using high-resolution capillary gas-liquid chromatography, and centered log ratio (clr) transformation was applied to the data to control for constant sum constraint. A total of 29 FAs were included for individual FA analysis and analysis of FAs grouped based on chemical or correlational properties determined by principal component analysis (PCA). The association of maternal allergy with FA concentrations were estimated using multiple linear regression.

Results: The PCA results did not show any clear associations of any maternal allergy indicator with overall breast milk composition at any time point. However, further analysis of clr transformed individual FAs showed that the metabolic and *delta-6-desaturase* indices in breast milk were significantly lower in mothers with asthma (with or without hay fever) in crude and adjusted models. At 6 weeks and 6 months, linoleic acid (LA) and total n-6 PUFAs were higher in breast milk of mothers with allergic disease but statistical significance disappeared upon adjustments. Similar to some previous studies, very small but significant differences were also observed when using untransformed individual FAs.

Conclusion: Our results suggest the plausibility of an impaired *delta-6-desaturase* enzyme activity converting LA to γ-Linoleic acid, which has been implicated in atopic disease mechanisms. Moreover, observed differences in our results between clr transformed and untransformed FA data call for re-evaluation of previous as well as future studies using statistical methods appropriate for compositionality of FA data.

OA0127 | MiRNA and cytokines in breast milk may be associated with the development of allergic diseases in breast-fed infants

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Background: Maternal factors seem to influence the development of allergic diseases. However, the underlying mechanisms of maternal factors remain to be clarified. We hypothesized that miRNA and cytokines in breast milk may function as the maternal factors.

Method: Twenty-five exclusively breast-fed infants and their mothers were recruited. After taking informed consent from mothers, breast milk was collected on the day 3-5 after birth. MiRNAs were extracted by using mirVana miRNA PARIS kit, and the levels of miR-155, miR-21, and Let-7c were measured by qPCR. TSLP, IL-35, IL-10, and TGF-b1, and b2 in the milk were measured by ELISA. At 10 months of age, the infants' and mothers' allergic statuses, including food allergy, atopic asthma, allergic rhinitis and/or atopic dermatitis were assessed.

Results: The miR-155 levels were higher in the milk fed to allergic infants compared to non-allergic ones. The levels of miR-21, and TGF-b1, and b2 were elevated in the milk from allergic mothers having an allergic infant than that from non-allergic mothers having a non-allergic infant. However, there was no significant correlation between miR-21 and TGF-b levels. No significant differences were observed in the levels of Let7c, TSLP, IL-35, and IL-10 in the milk between allergic and non-allergic infants.

Conclusion: Taken together miR-155 and miR-21 have been shown to interfere the differentiation and function of Th1 cells and regulatory T cells, respectively, these two miRNAs in breast milk might facilitate the development of allergic disease. On the other hand, TGF-b1 is known to induce regulatory T cells and oral tolerance. Therefore, the elevated TGF-b in the milk from allergic mothers might reflect a compensatory phenomenon in terms of prevention of allergic diseases. Further studies are required to clarify the regulatory roles of miRNA and cytokines in the development of allergic diseases in breast-fed infants.

OA0128 | Serum periostin levels are associated with polysensitization and perinatal and postnatal factors in children

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Background: Previous studies have used serum periostin levels as a biomarker of Th2-driven inflammatory responses. However, no population-based study has yet examined the association of serum periostin levels with the allergic status of children. The aim of this study was to determine the relationship of serum periostin levels with sensitization to allergens and perinatal and postnatal factors in 7 years old children.

Method: This prospective cross-sectional study examined 451 children enrolled from the general pediatric population who were at 6 different schools between June and July 2016. Of the 451 children with aged 7 years, 249 children with questionnaire data, skin prick test, and blood samples were included for the final analysis.

Results: The geometric mean serum periostin level was 107.6 ng/mL (95% confidence interval [CI]: 104.5-110.7). After adjustment for confounding, serum periostin levels were significantly associated with sensitization to poly-allergens (adjusted odds ratio [aOR] = 1.032, 95% CI: 1.006-1.059, P = .016) and pollen (aOR = 1.020, 95% CI: 1.002-1.039, P = .026). Serum periostin level were also associated with eosinophil level (adjusted β = .023, SE = 0.009, P = .010), exposure to secondhand smoke during pregnancy (aOR, 1.083, 95% CI 1.005-1.168, P = .036), and weaning before 6 months (aOR 1.098, 95% CI 1.025-1.176, P = .008), but was unrelated to body mass index, sex, obesity, or presence of an allergic disease.

Conclusion: Serum periostin levels may affect the severity and subphenotypes of allergic diseases in 7 years old children.

OA0129 | The dynamics of antimicrobial peptide expression in pediatric atopic dermatitis

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Background: Antimicrobial peptides (AMPs) play an essential part in maintaining the balanced innate immune functions of the skin barrier. Changes in their ratio and quantity may result in a microbiocenosis imbalance and a growing atopic dermatitis severity. To study the changing expression of Dfs profiles in the course of anti-inflammatory external therapy in children with atopic dermatitis.

Method: This study enrolled 10 children with atopic dermatitis, av. age 4.4 ± 2.5, severe AD, the average SCORAD 57.5 ± 5.4. The patients received anti-inflammatory therapy leading to a decrease in SCORAD by an average of 31.2 ± 5.2.

The control group consisted of 14 healthy children . The skin smear seeding was performed on blood agar. The isolates obtained were identified according to conventional microbiological tests. Skin smears were taken simultaneously from healthy and affected areas before external therapy (69 research). In the skin samples (keratinocytes) for detection of expression of HBD-1, HBD-2, HBD-3 and HNP-1 gens we used the methods of RNA extraction (kit "AmpliPRIME RIBOsorb", InterLabService, RF), reverse transcription reaction ("OT-1", Sintol, RF) and real-time PCR technique (DT-96 amplificator, DNA-Technology, RF with a standard SYBR Green I RT-PCR kit and primers synthesized by Sintol, RF). The statistical data processing was carried out using Stat Soft "Statistica 8.0. The data were presented as median. The Mann-Whitney non-parametric test was used to calculate statistically significant differences in the study groups.

Results: While being under treatment 60% of patients (staphylococci not detected) demonstrated similar dynamics when a decreasing SCORAD was followed by an increase in HBD-2 and HBD-3 by 3 and more times up to normal (5595 and 671 respectively), and HNP-1 evened out. 20% (with staph.epidermidis detected) manifested a moderate rise in HBD-2 expression both in lesions and healthy skin and HBD-3 expression dropped to almost none. The rest of the patients (with staph.aureus infected) showed an insignificant increase in HBD-2 and HBD-3 expression and their values were statistically lower than the ones from the healthy control group. In lesional skin HNP-1 increased threefold and did not change during the treatment; in healthy skin areas, it returned to normal (5,7).

Conclusion: Therefore, we can conclude that the dynamics of defensins expression may depend not only on the efficacy of anti-inflammatory external therapy but also on skin colonization by various staphylococci.

OA0130 | Correlation between intestinal barrier dysfunction and epigenetic activation of atopy in children with food hypersensitivity skin symptoms

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Background: Aim of the study was to assess correlation between intestinal barrier dysfunction and epigenetic activation of the atopy in children with Food hypersensitivity (FH) skin symptoms.

Method: 424 patients aged 26, 28 [12.00; 54.25] months with skin symptoms of FH participated in the study. Intestinal barrier function was assessed with the urine lactulose test (ULT), hydrogen breath test with glucose (H2) and fecal calprotectin (FC) detection in the coprofiltrate. Expression of the transcription regulators GATA-3 and FOXP3 (RayBiotech, Inc., USA), STAT6 (Elabscience Biotechnology Co., Ltd., China) was detected in monocytes with ELISA method.

Results: Transcription factors expression varied with age. STAT-6 was detected in 94.59%, n = 35/37 of children at age 24[13;36]

months, then signs of activation of differentiation of lymphocytes was observed (GATA-3 (54.05%, n = 20/37)) at age 39[17;77] months, and number of cells with activated FOXP-3 (21.62%, n = 8/37) increased at age 88[52;129] months. Association of GATA-3 with age of patients up to 4 years (φ=0.085, $P < .05$) and positive results of skin tests (φ=0.11, $P < .05$) was revealed, but correlation with age of debut and the duration of symptoms persistence ($P > .05$) were not confirmed. 64.28% (n = 99/154) of patients had signs of intestinal barrier dysfunction (lactulose in urine 2.58 [1.87;3.15] mmol/l). 40.77% (n = 42) and 45.09% (n = 46) of children had positive result of the H2 and positive FC. The vast majority of these patients (2/3) were related to early childhood (up to 3 y.o). Correlation analysis showed that the age of children cannot be a prognostic factor for assessing the degree of permeability of the mucosal barrier (determination coefficient $R^2 = .06$).

ULT was associated with activation of the STAT-6 (φ=0.079, $P < .05$), positive H2 breath test—with presence of GATA-3 (φ=0.118, $P < .05$). Children with activated FOXP-3 had lower urine lactulose level 0.7 [0; 1.22] mmol/l, compared to the children with negative FOXP-3 test (2.29 [1.05; 3.21] mmol/l, $P < .05$).

Conclusion: Increase of the permeability of the intestinal barrier is an early sign of the epigenetic activation of Th2. Disappearance of the pathological permeability of the intestine is a prognostic marker of the expression of FOXP-3.

OA0131 | The role of gene polymorphisms and serum levels of growth factors in the immunopathogenesis of atopic diseases in children

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Background: To study the role of vascular endothelial growth factor (VEGFA) and transforming growth factor β1 (TGF β1), as well as polymorphic variants of their genes in the pathogenesis of allergic diseases in children.

Method: 152 children with allergic diseases were examined: group I—60 children with bronchial asthma, group II—26 patients with atopic dermatitis and group III—66 patients with bronchial asthma was combined with atopic dermatitis. The control group consisted of 122 healthy children. The relationship between the association of polymorphic loci *Arg25Pro* of *TGF β1* and *C634G* of *VEGFA* gene with the risk of disease development was analyzed. Polymorphic variants of the studied genes were determined by allele-specific polymerase chain reaction using SNP-Express reagent kits. Blood tests for immunological parameters were performed with the enzyme immunoassay with the use of sets Human TGF beta 1 Platinum ELISA Human VEGF-A Platinum ELISA (Austria).

Results: It's been established that children with allergic disease have significantly higher the concentration of TGF β1 in comparison with the control group [2.70 ± 0.12 PG/ml ($P = .01$)], while in patients of group I – 159.76 ± 101.95 PG/ml, II – 193.81 ± 60.76 PG/ml and III – 130.66 ± 59.96 PG/ml. Also an increase in the level of VEGF in serum of patients: in group I – 121.77 ± 21.46 PG/ml, II – 216.915 ± 44.27 PG/ml, III – 125.58 ± 20.49 PG/ml. At the same time, the correlation relationship was revealed between the severity of allergic diseases and the level of growth factors in the serum of patients. Association of *Arg25Pro* polymorphisms of *TGF ß1* and *C634G* of *VEGFA* gene with increased risk of bronchial asthma development was established. The frequencies of alleles and genotypes of *Arg25Pro* of *TGF-β1* gene in group III patients are also significantly different from those of the control group ($P < .001$): the predominant homozygotes of *Arg25*-allele, while the frequency of *Arg25Pro* heterozygotes is significantly lower.

Conclusion: It should be assumed that VEGFA and TGF β1 are biological markers of allergic diseases in children. Patients who are homozygotes for *Arg*-alleles of the *TGF-β1* gene and heterozygotes for polymorphism *C634G* of the *VEGFA* gene have a high predisposition to the development of not only bronchial asthma, but also combined forms of allergic diseases.

TUESDAY, 4 JUNE 2019
OAS 23
NOVEL APPROACHES OF ALLERGEN IMMUNOTHERAPY

OA0132 | A novel Pru p 3 sublingual immunotherapy ultra-rush protocol

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Background: Sublingual immunotherapy (SLIT) with Pru p 3 is an effective treatment to prevent severe allergic reactions to LTP-containing foods. The standard initiation protocol is safe but time-consuming.

Method: Prospective study to compare tolerance and side effects of a novel ultra-rush protocol (UR) versus the standard initiation (SI) of SLIT with Pru p 3. Patients were divided into group A, which underwent de SI protocol with a total duration of 4 days, and, group B, that underwent the UR with a total duration of 2 days. The cumulative allergen dose in the build-up phase was 47 µg in the UR group and 78 µg in the SI group, up to the daily maintenance dose of 10 µg of Pru p 3 for both groups.

Results: Fifteen patients were included (5 in the SI group and 10 in the UR initiation), 80% females, median age of 23.4 years-old and 73% were atopic. All patients were polysensitized to several LTP-containing foods, except for one patient monosensitized to peach. All patients had at least one episode of anaphylaxis, and peach was the most frequently implicated food (5/15), followed by tomato (3/15) and pear (2/15). Co-factors were present in 3 patients. All patients had positive SPT to commercial peach extract (average weal of 7 mm), 8 patients had positive prick-to-prick tests with peach skin and pulp (average weal of 8 and 7 mm, respectively) and 11 were positive to Pru p 3 extract (average weal of 10 mm). The initial average concentration of sIgE to peach and Pru p 3 was 22.9 kU/L (min. 1.13 kU/L, max. >100 kU/L) and 23.3 kU/L (min. 1.69 kU/L, max. >100 kU/L), respectively. Twelve months after SLIT initiation, sIgE concentrations to peach averaged 15.8 kU/L, having increased in 3 patients, all from the UR group, and decreased in 8 patients. The average sIgE to Pru p 3 after 12 months of treatment was 20.3 kU/L, with increased concentrations observed in 4 patients, 3 of which from the UR group. All patients from both groups had oropharyngeal pruritus during initiation, 80% with spontaneous recovery and no systemic side effects were observed. Only 1 patient with the SI protocol reported an episode of urticaria during exercise after the ingestion of apple with skin occurring 1 year after stopping treatment. There were no new episodes of anaphylaxis reported.

Conclusion: In our case series, both the SI and the novel UR protocols for the initiation of SLIT with Pru p 3 were safe and well-tolerated. The novel UR protocol reduced the build-up phase to half the time, without increasing side effects.

OA0133 | Strong dose-response using a conjunctival provocation test during a phase II allergen immunotherapy study with subcutaneously administered tyrosine adsorbed modified grass allergen + MPL

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Background: This Phase II study [EudraCT 2017-000333-31] evaluated the dose response relationship for a modified grass subcutaneous immunotherapy (SCIT) product with modified allergen tyrosine adsorbate (MATA) and monophosphoryl lipid A (MPL) adjuvants for allergic rhinoconjunctivitis (ARC) due to grass pollen.

Method: In total 447 patients were enrolled in this randomized, double-blind, placebo-controlled, parallel group study. Patients were randomized to one of five dose regimens of 5100, 14400, 27600 and 35600 SU and placebo. The primary endpoint was the total symptom score (TSS) as measured during a conjunctival provocation test (CPT). Three dose response models were predefined: an Emax, logistic, and linear in log-dose model. MCP-Mod was used to characterize a dose response relationship.

Results: For all three individual pre-specified dose response models, a highly statistically significant dose-response ($P < .0001$) was shown for the range of cumulative doses from 5100 SU to 35600 SU. The dose reaching at least 50% of the full CPT effect size over placebo (ED50) was approximately 2900 SU, in support of the currently marketed cumulative dose of 5100 SU in Europe, which is almost 2-fold higher. All doses evaluated were well tolerated.

Conclusion: This study demonstrates a clear and statistically significant dose response on TSS following CPT after an ultra-short course of 6 injections with allergoid grass SCIT treatment with adjuvants MATA and MPL. Both the cumulative 27600 SU and 35600 SU doses showed a similarly optimal risk/benefit profile. Either dose may therefore be selected for further investigation in pivotal phase III studies.

OA0134 | Immunomodulatory properties of lolium perenne peptides for the treatment of seasonal allergic rhinitis

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Background: Short linear allergen peptides do not cross-link IgE receptor on the surface of mast cells and basophils. They are thought to have a superior safety profile for immunotherapy. We hypothesized that *Lolium Perenne* peptides (LPP) derived from enzymatic hydrolysis would have reduced allergenicity, Th2A and T follicular helper (Tfh) cell responses and can promote B regulatory (Breg) and blocking antibody responses.

Method: Peripheral blood monocular cells (PBMCs) from 16 grass pollen allergics (SAR) and 6 non-atopic controls (NAC) were stimulated with several candidate peptides and native grass pollen protein. The allergenicity of the LPP candidates was measured by their ability to activate basophils and promote histamine release using flow cytometry. Allergen-specific Tfh cells and IL-10$^+$ Breg cells were also quantified by flow cytometry.

Results: We have previously shown in a multicenter Phase III RDBPCT that short-course LPP immunotherapy resulted in the reduction of CSMS in LPP-treated group, compared to placebo group (P = .041 and P = .029) in and out of the peak pollen season, respectively. To elucidate the underlying mechanism of action, the effect of several candidate peptides was further investigated. Native grass pollen protein elicited a dose-dependent increase in basophil responsiveness as illustrated by CD63$^+$CRTH2$^+$ (EC_{50}=22.93 ± 7.27 ng/mL), CD203c^{bright}CRTH2$^+$ (EC_{50}=12.50 ± 4.45 ng/mL), DAO$^-$ CD63$^+$CRTH2$^+$ (EC_{50}=97.62 ± 59.58 ng/mL) and DAO$^-$ CD203c^{bright}CRTH2$^+$ (EC_{50}=106.70 ± 59.07 ng/mL) basophils in SAR, but not NAC. All candidate peptides illustrated reduced allergenicity when compared to native grass pollen protein (all, P < .01). In addition to this, all candidate peptides induced CD19$^+$CD5$^+$CD27$^+$IL-10$^+$ (P = .0085) and CD19$^+$CD5$^+$CD38^{int}CD24^{int}IL-10$^+$ (P = .0468) Breg cell subsets compared to native protein in SAR. Furthermore, all candidate peptides were able to elicit less proliferation of CD4$^+$ T cells, Th2A cells, Tfh cells, ICOS$^+$ Tfh cells, IL-4$^+$, IL-21$^+$ and IFN-γ$^+$ Tfh cells (all, P < .05) compared to native protein.

Conclusion: For the first time, we demonstrate that candidate *Lolium Perenne* peptides have reduced allergenicity. In addition, reduced Th2A responses and enhanced IL-10$^+$ Breg responses were also elicited by candidate *Lolium Perenne* peptides.

OA0135 | Allergoids conjugated to mannan drive monocyte differentiation into tolerogenic dendritic cells and anti-inflammatory macrophages

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Background: Allergen-specific immunotherapy (AIT) is the single curative treatment for allergy, but it still faces problems related to efficacy, security, duration and patient compliance. Glutaraldehyde-polymerized grass pollen allergoids conjugated to non-oxidized mannan (PM) represent next-generation vaccines for AIT targeting dendritic cells (DCs) that promote the generation of forkhead box P3 (FOXP3)$^+$ regulatory T (Treg) cells. The aim of this study was to investigate the impact of PM over the monocyte differentiation process into DCs and macrophages (MØ)

Method: Monocytes were differentiated in the presence of IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) to obtain human monocyte-derived DCs (hmoDCs), with GM-CSF to obtain GM-MØ, or with macrophage colony-stimulating factor (M-CSF) to obtain M-MØ. PM was added at days 0 and 4 of the differentiation to obtain PM/hmoDCs or PM/GM-MØ. The expression of surface markers and cytokine signature were determined by flow cytometry, qPCR or ELISA. Allogeneic cocultures of PM/hmoDCs with naïve CD4$^+$ T cells were performed to analyse T cell polarization. Frequencies of FOXP3$^+$ Treg cells were quantified. Blocking and pharmacological inhibition experiments were performed in PM/hmoDCs.

Results: HmoDCs generated in the presence of PM are characterized by a significantly lower cytokine production after LPS stimulation (TNF-α, IL-6 and IL-1β), higher IL10/TNF-α, IL-10/IL-6 and IL-10/IL-1β ratios, and a higher expression of the tolerogenic molecules *PDL1*, *IDO*, *SOCS3* and *IL10* than hmoDCs generated in the absence of PM. PM/hmoDCs also show a higher capacity to promote the generation of FOXP3$^+$ Treg cells than hmoDCs generated without PM. Blocking experiments suggest that the inhibition of indoleamine-2,3-dioxygenase (IDO) reduces the induction of FOXP3$^+$ Treg cells by PM/hmoDCs. Furthermore, human GM-MØ differentiated in the presence of PM acquired an immunosuppressive-like profile similar to the profile of M-MØ. PM/GM-MØ are characterized by a remarkable production of IL-10 after LPS stimulation and a high expression of *CD163*, *CCL2*, *IL10* and CD14 macrophage markers.

Conclusion: Our results demonstrate that allergoids conjugated to non-oxidized mannan modulate monocyte differentiation by promoting tolerogenic DCs and anti-inflammatory macrophages, which might also well contribute to the generation of healthy immune responses to allergens induced by these next-generation vaccines.

OA0137 | A novel toll-like receptor 7 agonist can ameliorate phleum pratense induced allergic responses in vitro

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Background: Administration of Toll-like Receptor (TLR) agonists during allergen immunotherapy (AIT) has been demonstrated to enhance the onset of tolerance. TLR7 in particular has associations with asthma and allergy making it a suitable target for novel treatments. We hypothesised that a novel synthetic agonist targeting TLR7 can modulate T_H2 mediated allergic inflammation to a more favourable T_H1 immune response in an *in vitro* model.

Method: PBMCs were obtained from seasonal allergic rhinitis (SAR) patients (n = 19) recruited during the grass pollen season. PBMCs were stimulated with *Phleum pratense* (Phlp) allergen at 10 μg/mL and dose ranging concentrations of TLR7-01 for 6 days. Target engagement of TLR7-01 was confirmed through Luminex MagPix assay for IFNα production after 24 hours. Cytokine production associated with T_H1, T_H2 and T regulatory cell (Treg) responses was measured at day 6 with proportions of IL-4^+ T_H2 cells, IFNγ^+ T_H1 cells and IL-10^+ Tregs quantified via flow cytometry. Finally, pan-dendritic cells (DCs) were isolated and cultured with Phlp and TLR7-01 for 24 hours before washing and co-culture with memory $CD4^+$ cells for 7 days.

Results: TLR7-01 induced IFNα in a dose-dependent manner and was unaffected by the presence of Phlp, with a maximal response obtained at 10 μM ($P < .001$). PBMCs exposed to TLR7-01 at 10 μM induced a four-fold reduction in Phlp induced IL-5 and a two-fold reduction in IL-13 production (both, $P < .001$). Additionally, the proportion of IL-4^+ T_H2 cells were reduced following TLR7-01 exposure ($P < .05$). IL-12p70, IL-27 and IFNγ production was significantly enhanced following exposure to TLR7-01 (all, $P < .001$), although the proportion of IFNγ^+ T_H1 cells was unaffected. IL-10 production was significantly enhanced with TLR7-01 exposure ($P < .001$) whilst the proportion of $CD4^+$IL-10^+ Tregs remained unaffected. Interestingly, the proportion of $CD4^-$IL-10^+ cells (non-CD4 T cells) were increased ($P < .05$). Finally, Pan-DCs primed with TLR7-01 and Phlp reduced the proportion of IL-4^+ T_H2 cells to Phlp alone.

Conclusion: We demonstrated for the first time that TLR7-01 and grass pollen antigen inhibit pro-allergic IL-5 and IL-13 responses while promoting IFNγ and IL-10 production. The utility of the immunomodulatory effect of TLR7-01 needs to be validated in a larger cohort study.

TUESDAY, 4 JUNE 2019
OAS 24
ATOPIC DERMATITIS FROM BENCH TO BEDSIDE

OA0138 | In vivo raman spectroscopy discriminates between filaggrin loss-of-function carriers vs. wild-type in day 1-3 neonates

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Background: Carriers of loss-of-function mutations in the filaggrin gene (LoF *FLG*) have reduced levels of natural moisturising factor (NMF) in their stratum corneum (SC) and an increased risk of atopic dermatitis (AD). NMF measured by Raman spectroscopy has been shown to accurately stratify older children [mean (SD) age 8 (4) years] by *FLG* genotype. The use of Raman-derived NMF at birth as a predictive test for *FLG* genotype could inform targeted prevention of AD, but values in the neonatal population are largely unexplored.

Method: NMF [g/g of protein] was measured by Raman Spectroscopy at a depth of 20 + /- 5 μm in the SC of the thenar eminence within 4 days of birth (90% aged 1-3 days) in 141 term neonates. Eighty-three neonates (59%) had their *FLG* genotype investigated using a targeted array-based sequencing approach.

Results: The mean (SD) neonatal NMF concentration of 0.36 (0.11) g/g protein was lower than published values for older children and adults, with mean NMF content increasing with age in days [Day 1 vs. Day 3: 0.29 (0.09) vs.0.43 (0.08) g/g protein, $P < .001$]. Ten infants (12%) were carriers of LoF *FLG*, all of whom were heterozygous for the mutation. NMF concentrations were significantly lower in LoF *FLG* carriers compared with wild type [0.26 (0.08) vs. 0.38 (0.11) g/g protein, $P \leq .001$]. NMF had good discriminatory power for *FLG* genotype in neonates [area under the receiver operating curve (ROC), 0.82; 95% CI, 0.71, 0.94]. Based on ROC curve analysis, the optimal cut-off value for mean NMF to distinguish by *FLG* genotype was 0.28 g/g protein, with a sensitivity of 80% and a specificity of 80.8%.

Conclusion: NMF concentrations are still stabilising during the first week of life. Despite this, Raman-derived NMF measured in the first 3 days of life can discriminate between LoF *FLG* carriers and wild type and has the potential to identify neonates at high risk of developing AD. Future studies should examine whether the predictive accuracy of neonatal NMF increases over the longer neonatal period and if it tracks with AD itself, as has been shown in older children. It might also prove possible to further increase predictive value by the use of different NMF-threshold values at different days after birth.

OA0139 | Eosinophil count, serum CCL17/18/26 and IgE levels in atopic dermatitis: Upadacitinib phase 2 study analysis

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Background: Upadacitinib (UPA), a selective JAK1 inhibitor, is being investigated for the treatment of atopic dermatitis (AD). This analysis assessed the impact of UPA treatment on absolute eosinophil count (AEC), serum levels of CCL17, CCL18, and CCL26, and serum total and antigen-specific IgE levels in patients with AD.

Method: Adults with moderate-to-severe AD were randomized to daily placebo or UPA 7.5, 15, or 30 mg in a 16-wk, phase 2 study. Wk 16 AEC, CCL17/18/26 levels, and total as well as antigen-specific IgE (ImmunoCap) serum levels were analyzed along with changes in Eczema Area and Severity Index (EASI) and pruritus numeric rating scale (NRS, weekly average of daily patient assessments). Statistical analysis was done using analysis of variance and Spearman correlation.

Results: Mean percentage improvements from baseline to wk 16 in EASI (39.4%/61.7%/74.4% vs 23.0%; $P < .05/<.001/<.001$) and pruritus NRS (39.6%/48.0%/68.9% vs 9.7%; $P < .01/<.001/<.001$) were significantly greater with UPA 7.5/15/30 mg vs placebo. Wk 16 AEC was significantly lower with 30 mg UPA vs placebo ($P = .01$); significant differences were observed as early as wk 2 in UPA 15-mg ($P = .003$) and 30-mg groups ($P < .0001$) vs placebo. Percentage change from baseline to wk 16 in AEC correlated with percentage changes in EASI ($r = .56$, $P < .0001$) and pruritus NRS ($r = .64$, $P < .0001$). Wk 16 serum levels of CCL17/18/26 were significantly lower with 30 mg UPA vs placebo ($P = .01$); significant differences vs placebo were observed as early as wk 2 in UPA 15-mg ($P = .003$) and 30-mg groups ($P < .0001$). Serum protein levels of CCL17/18/26 correlated with EASI ($r = .48/.63/.60$, $P < .05$) and pruritus NRS ($r = .42/.53/.50$, $P < .05$), and changes from baseline to wk 16 in CCL17/18/26 with UPA 7.5/15/30 mg vs placebo correlated with percentage changes in EASI ($r = .36/.50/.49$, $P < .05$) and pruritus NRS ($r = .37/.41/.46$, $P < .05$). There were no trends in antigen-specific or total IgE levels as a function of study duration, and no clear relationship between levels and improvements in AD (EASI or pruritus NRS).

Conclusion: Eosinophil counts and serum levels of Th2-attracting chemokines (CCL17/18/26) were significantly reduced with UPA treatment (15/30 mg) as early as wk 2, suggesting that UPA may

have early and robust effects on the Th2 and eosinophil axis. No significant changes in total and specific IgE levels were observed, suggesting that UPA clinical efficacy is independent of IgE levels, perhaps arguing against its role in AD pathogenesis.

OA0140 | The importance of patch testing in drug reaction with eosinophilia and systemic symptoms 10 years after

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Background: DRESS is a severe cutaneous adverse drug reaction due to hypersensitivity to a drug and common reactivation by other factors (virus and other drugs). Hypersensitivity to the culprit drug(s) can be confirmed by a positive patch test (PT) but this varies according to the culprit drug(s). Objectives: Evaluate the value of PT in DRESS in the last 10 years, in comparison with our study in the preceding 10 years.

Method: From 2009 to 2018, patients with DRESS according to the RegiSCAR criteria performed PT at the Dermatology Department of Coimbra University Hospital, with the main culprit drug(s) and all drugs administered concomitantly or suspected of inducing DRESS flares. Drugs at 1-10% pet (Chemotechnique diagnostics®) or from a commercial preparation diluted at 10% pet were patchtested according to ESCD guidelines.

Results: We studied 41 patients (20 male/ 21 female, mean age 53 years). The main culprits were allopurinol (15), antiepileptics (14), trimethoprim/sulfamethoxazole (4), salazopyrine (3), diclofenac (2), antiretrovirals, ezetimibe/simvastatin and strontium ranelate (1 each). In 15 patients other drugs (18) were suspected of worsening DRESS, amoxicillin (8), ciprofloxacin (2), cefoxitin (2), levofloxacin, ceftriaxone, ceftazidime, vancomycin, acyclovir and metamizole (1 each).

A positive PT to the culprit drug was observed in 10 patients (24.3%), all to antiepileptics. Positive reactions were observed to drugs related with flares in 12/18 suspected drugs (67%): amoxicillin (6), cephalosporins (3), vancomycin (1), acyclovir (1) and metamizol (1), but not to quinolones (3).

Conclusion: Results were similar to the study conducted 10 years before when 18/56 (32.1%) patients had positive PT, mostly to carbamazepine and other anticonvulsants and no positive reaction to allopurinol. Distinct from our previous study, when no tests were performed with the antibiotic series or other drugs used after the initiation of DRESS, we showed that PT can be a valuable tool to diagnose co-sensitisation in DRESS and emphasise the importance of testing all medications taken during the whole episode, even when PT has no value for the main culprit drug, like allopurinol. Recognising a co-sensitisation can prevent a new DRESS induced by the second drug.

OA0141 | Treatment satisfaction in patients receiving dupilumab for moderate-to-severe atopic dermatitis

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Background: Dupilumab is a novel and effective therapeutic option for patients suffering from moderate-to-severe atopic dermatitis (AD). Dupilumab induces clinical meaningful changes in multiple patient-reported outcomes, such as pruritus and quality of life. However, the effects of dupilumab on patient's treatment satisfaction during dupilumab treatment have not yet been studied, specifically the patient-reported outcomes regarding convenience, effectiveness, side-effects and global satisfaction. With such a novel treatment it is of value to have quantifiable insights regarding the patient's experiences. This study aims to assess treatment satisfaction of patients receiving dupilumab for AD.

Method: In a prospective daily clinical practice registry (BioDay) we included all patients receiving dupilumab for 16 weeks between September 2018 and January 2019 at the University Medical Centre Utrecht, Utrecht, The Netherlands. We utilized the Treatment Satisfaction Questionnaire for Medication version II (TSQM), a universal, multi-linguistically validated questionnaire developed to measure patient satisfaction for medications. The TSQM encompasses 4 key domains assessing; global satisfaction, efficacy convenience, and side-effects. Scores are expressed in percentages and range from 0 (least satisfied) to 100 (most satisfied).

Results: During the course of this study 52 patients, of which 62% male with a median age of 43 years, completed the TSQM. The median (interquartile range) EASI (Eczema Area and Severity Index) improved from 15 (10-14) to 3 (1-6) after 16 weeks. The median (interquartile range) domain scores were: convenience 78% (67-93); global satisfaction 83% (67-92); effectiveness 83% (67-100); side-effects 100% (94-100). The proportion of patients that experienced side-effects was 29 (56%). In comparison to patients without side-effects, patients who experienced side-effects scored significantly higher in the effectiveness domain (P = .035) and lower in the side-effects domain (P = .028). When compared, patients who experienced side-effects did not have a significantly different EASI at baseline or after 16 weeks. There were no significant differences in the global satisfaction and convenience domains between patients who did and did not experience side-effects.

Conclusion: Our results show that patients receiving dupilumab in daily clinical practice are very satisfied with their overall experience, regardless of whether or not they experience side-effects.

OA0142 | Conjunctival inflammation and loss of goblet cells in atopic dermatitis patients treated with dupilumab in daily practice

Bakker DS[1]; Ariëns LF[1]; Van Luijk C[2]; Balak DM[1]; Thijs JL[1]; Van Der Schaft J[1]; Schuttelaar MA[3]; Wisse RP[2]; Knol EF[1,4]; Koenderman L[4,5]; Vercoulen Y[4]; Van Dijk MR[6]; Van Wijk F[4]; De Bruin-Weller MS[1]

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Background: Dupilumab is a human monoclonal antibody targeting the interleukin-4 receptor alpha and thereby inhibiting the signals of interleukin-4 and interleukin-13 showing very promising results in the treatment of moderate to severe atopic dermatitis (AD) with a favorable safety profile. However, relatively high rates of conjunctivitis have been reported during dupilumab treatment. The pathomechanism underlying the development of conjunctivitis during dupilumab treatment has not yet been clarified. The aim of this study was to elucidate the mechanisms underlying the development of conjunctivitis during dupilumab treatment in patients with atopic dermatitis using innovative experimental techniques.

Method: In this case series study moderate-severe AD patients developing a confirmed conjunctivitis during dupilumab treatment and in whom a diagnostic conjunctival biopsy was performed, were included for further analysis. Complete standardized ophthalmological examination was performed. Diagnostic biopsies from the tarsal conjunctiva were histopathologically analyzed by an experienced eye pathologist. Imaging Mass cytometry was performed on paraffin-embedded conjunctival tissue to perform functional profiling on infiltrating cells.

Results: On September 1st 2018 a total of six patients were included. The clinical severity of dupilumab-related conjunctivitis ranged from mild to severe. Conjunctival biopsies revealed scarcity of intraepithelial goblet cells accompanied by a T-cell and eosinophilic infiltrate in the conjunctival stroma. Imaging Mass Cytometry showed an activated CD4/CD8 + T cell infiltrate with cytotoxic activity (Granzyme B) and extensive epithelial activation (pS6) with IL-10 production.

Conclusion: Our findings indicate that dupilumab-related conjunctivitis is marked by goblet cell scarcity in the conjunctival epithelium accompanied by an inflammatory infiltrate, consisting of eosinophils and activated CD4/CD8 T cells showing cytotoxic activity. However, the exact underlying pathomechanism of this new entity of conjunctivitis remains unknown. A prospective study to further characterize conjunctivitis in AD patients before and during dupilumab treatment will be started soon.

OA0143 | Polyprenol alone in atopic dermatitis management

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Background: Dysregulation of DPAGT1 (Dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (GlcNAc-1-P transferase) causes disturbances in filaggrin expression. The resent results are in favour of the idea that N-glycosylation in keratinocytes cells is limited by Dolichyl Phosphate Cycle (DPC) intermediates which could prevent cell-mediated cytotoxicity against skin fibroblasts in atopic dermatitis (AD). In our earlier work (2012) we have demonstrated approach of AD treatment with the use of the Atorvastatin and Polyprenol (PP).The aim of the present study is to investigate the effect of high dose of PP alone, which provides a dolichol phosphate (DolP) substitute on regulation of filaggrin expression.

Method: SCORAD index was used to measure the severity of the disease and to evaluate the effect of treatment in 125 adult patients. Evaluation of erythema, induration, excoriation, lichenification, scaling, erosion were scored on a 0 to 3 scale each week. A 30% decrease in total score was considered clinically significant. Leukotriene E4 and dolichol (Dol) were assayed in urinal excretion, immunoCAP total IgE levels were measured in serum . Filaggrin expression was measured in skin biopsies Filaggrin expression was measured in skin biopsies and cultured keratinocytes using real-time RT-PCR and immunohistochemistry. PP (20 mg/day, per os) was given in a randomized, double-blind, placebo-controlled study. The effect of the treatment was evaluated weekly up to six months.

Results: Initially, patients with AD were found to have a statistically significant increase in leukotriene E4 (4-fold) and Dol (6.2-fold) excretion, total Ig E level and GPT activity in fibroblasts in comparison to controls. Compared with normal skin, filaggrin expression was significantly reduced ($P < .01$) in AD skin. Overexpression of DPAGT1 was 5-fold higher in AD skin biopsies than in normal skin biopsies and differ from normal one in filaggrin content lost by 3-4 times. The normalization up to 90% of Dol excretion was achieved after 2 weeks of treatment, IgE and E4 in 3 weeks, GPT after one month in 68 % of patients with remission for more than one year. Significant difference in AD scores between PP and placebo ($P < .01$) was recognized.

Conclusion: The present study demonstrates alleviation of AD with the use of the PP which could present novel therapeutic options in the management of atopic dermatitis.

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MECHANISMS AND MANAGEMENT OF DRUG HYPERSENSITIVITY

OA0144 | Synthetic antigenic determinants of clavulanic acid can induce maturation of dendritic cells in immediate allergic reactions to this drug

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Background: Selective reactions to clavulanic acid (CLV) account for around a 30% of immediate reactions to amoxicillin-CLV combination. CLV degradation pathways are very complex and the precise antigenic determinants (AD) recognized by the immune system are not known. To know the AD able to induce the allergic reaction is crucial to improve the diagnostic methods. Therefore, our aim was to evaluate the recognition of different synthetic determinants of CLV by dendritic cells (DCs) and its capacity to induce the upregulation of different maturation markers.
Method: We have proposed the generation of to potential AD following the current knowledge about CLV degradation pathways. 3 structures were synthesized from each AD: AD-I (CLV1-3) and AD-II (CLV4-6). Peripheral blood mononuclear cells were collected from 10 patients with selective reactions to CLV and 10 tolerant subjects and immature DCs (moDCs) were derived from monocytes. CCR7, CD40, CD80, CD83 and CD86 expression were analyzed by flow cytometry after culturing the moDCs with the 6 different synthetic structures.
Results: The expression of CCR7, CD40, CD80 and CD83 were significantly upregulated in moDCs cultured with CLV2, CLV3 and CLV6 compared to controls, whereas with CLV we did not observe any significant modification in the evaluated markers. The inclusion of CLV1, CLV4 and CLV5 did not significantly upregulate any marker. No difference was shown in the expression of CD86 in any case.
Conclusion: Synthetic analogs of CLV with capacity for join proteins, CLV2, CLV3 and CLV6, induced a greater upregulation of maturation markers than CLV and those analogs without this capacity. The inclusion of these reactive analogs from both AD could be used to improve the sensitivity of *in vitro* assays and the diagnosis of these reactions.

OA0145 | Characterization of amoxicillin- and clavulanic acid-specific T-cells in patients with amoxicillin-clavulanic acid hypersensitivity reactions

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Background: Betalactam antibiotics are the most frequently prescribed antibiotics to treat infections. However, they are the most common cause of drug hypersensitivity reactions mediated by a specific immunological mechanism. Amoxicillin (AX) is the most often elicitor, which was originally prescribed alone, and is now often prescribed alongside clavulanic acid (Clav). The diagnosis is complex, based on skin testing and drug provocation test, methods not risk-free. In vitro testing can be used; however, their sensitivity is low, probably due to the use of chemical structures that are not optimally recognized by the immune system. The aim of this study was to generate and characterize AX- and Clav-specific T-cell clones from blood of hypersensitive patients to be used as tool to study the immunological recognition of new chemical structures derived from AX and Clav to be included in in vitro diagnostic tests.
Method: Peripheral blood mononuclear cells (PBMC) were isolated from AX-Clav hypersensitive patients. Drug-specific T-cell clones were generated from PBMC by serial dilution and repetitive mitogen stimulation. Antigen specificity was assessed by measurement of proliferation and cytokine release using [3H]-thymidine release and IFN-γ and IL-13 ELISpot, respectively.
Results: 110 AX-specific and 96 Clav-specific T-cell clones were generated from 7 patients. Activation and proliferation of AX- and Clav-specific T-cell clones was dose-dependent, no cross-reactivity between AX and Clav was observed and they presented mainly with a CD4 + phenotype. AX- and Clav-specific T-cell clones required the presence of drug and antigen presenting cells to proliferate. Drugs were presented to CD4 + T-cell clones by MHC class II and to CD8 + T-cells by MHC class I. Finally, the highest level of cytokine secreted following drug treatment was IFN-γ, followed by IL-13, IL-5 and IL-10. Most clones expressed high levels of CD69, CCR4, CCR10 and CXCR3.
Conclusion: AX- and Clav-specific T-cell clones can be generated from AX-Clav hypersensitivity patients, with no cross-reactivity between AX and Clav. They are activated by AX or Clav only in the presence of antigen presenting cells, supporting the hapten hypothesis for the recognition and presentation of betalactam antibiotics. The specific T-cell clones generated are an immunologically characterized tool that can be used for the analysis of

new structures derived from AX and Clav to be included in in vitro diagnostic tests.

OA0146 | B cell proliferation assay unravels amoxicillin allergy

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Background: In clinical practice, the diagnosis of amoxicillin allergy relies on (i) the evaluation of the clinical symptoms and (ii) the analysis of amoxicilloyl-specific IgE. In particular, two different pools of IgE exist: the *bound pool* and *circulating pool*. On the one hand, the amount of specific IgE bound on mast cells is assessed through skin testing, using both skin prick and intradermal tests. On the other hand, the circulating pool of IgE is usually assessed with ImmunoCAP technique. Recently, in grass pollen allergic patients it has been demonstrated the existence of circulating allergen-specific B cells. These cells proliferate upon cognate allergen encounter. In amoxicillin-allergic patients and heathy controls, we assessed the presence amoxicillin-specific IgE (unbound) and the B cell proliferation in response to amoxicillin.

Method: *Amoxicillin-specific IgE:* circulating IgE levels were measured by ImmunoCAP technique, in serum samples.

Lymphocyte collection: peripheral mononuclear cells (PBMCs) were obtained from the patient and healthy donor buffycoats by dextran sedimentation, followed by centrifugation on Lymphoprep (Nycomed Pharma, Oslo, Norway) and hypotonic lysis of contaminating erythrocytes.

Proliferation assay: blood mononuclear cells were stained with carboxyfluorescein diacetate succinimidyl ester (CFSE) and cultured in the presence of amoxicillin at different concentrations. After 3-day culture, lymphocyte subsets were analysed by flow cytometry using: anti-CD3-Allophycocyanin or anti-CD19-Pacific Blue. Actively proliferating cells were distinguished by excluding cells with high CFSE fluorescence.

Results: Consistently with their clinical status, all the patients had high levels circulating *amoxicilloyl*-specific IgE. Interestingly, the proliferation of CD 19^+ cells in the presence of the amoxicillin was higher compared to the control. In contrast, $CD3^+$ cells did not show a higher proliferation rate when exposed to amoxicillin. In healthy donor, neither $CD19^+$ nor $CD3^+$ cells proliferated in response to amoxicillin.

Conclusion: We demonstrated that amoxicillin-allergic patients have a population of circulating amoxicillin-specific $CD19^+$ cells. These cells can be detected using flow cytometry and their proliferation in response to the cognate allergen can be analyzed using CFSE dye.

OA0147 | Strongly positive basophil activation with gelatin-containing vaccines for varicella, zoster, measles, mumps and rubella in patients with alpha-gal syndrome

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Background: The alpha-gal syndrome, a new type I allergy entity to the carbohydrate epitope galactose-α-1,3-galactose (α-gal), was first described in 2009. High concentrations of alpha-gal are mainly found in mammalian food products (e.g., beef, pork and venison). Apart from meat products alpha-galcan also be found in products containing gelatin of bovine or porcine origin. Recent case reports pointed to severe anaphylaxis in patients suffering from alpha-gal syndrome after vaccination with vaccines containing hydrolyzed gelatin. It was the objective of this study to evaluate if basophil activation tests (BAT) performed with such vaccines were positive in patients with alpha-gal syndrome.

Method: BAT was performed with different dilutions of gelatin-containing vaccines (attenuated varicella-zoster vaccine (VZ vaccine), attenuated varicella vaccine (V vaccine), MMR Sanofi Pasteur MSD, France; measles, mumps and rubella live vaccine (MMR vaccine), Chiron Behring, Germany) in two patients (2 females, 81 and 68 years old) with confirmed alpha-gal syndrome (patient A: anaphylactic reaction to 1.5 g cooked pork kidney in oral provocation test (OPT) and patient B: anaphylactic reaction to 18 g cooked pork kidney in OPT). Additionally, two healthy individuals without any previous medical history for allergies were tested.

Results: Patient A (highest basophil activation: 92.1% CD63 expression with undiluted VZ vaccine; 87.3% CD63 expression at a dilution of 1:25 for vaccine; 88.7% CD63 expression at a dilution of 1:125 for MMR vaccine) and B (highest basophil activation: 51.3% CD63 expression at a dilution of 1:5 for VZ vaccine; 62.5% CD63 expression at a dilution of 1:5 for V vaccine; 61.2 % CD63 expression at a dilution of 1:5 for MMR vaccine) both showed positive results for all tested vaccines. The two healthy controls did not show any basophil activation.

Conclusion: Both patients with confirmed alpha-gal syndrome showed strongly positive basophil activation for all tested vaccines whereas healthy controls remained negative. Although this test does not prove clinical relevance in real-life situations, these vaccines should be administered with caution in patients with alpha-gal syndrome. It has been postulated that gelatin or other nonprimate mammal-derived products are the triggers. Missing

information on the exact amount of gelatin in vaccines might be useful for better risk stratification. Also, BAT might be a useful additional diagnostic tool when it comes to screen for potential patients at risk.

OA0148 | Smartphone-based patient tailored drug allergy preventive system—Pilots study in 4 tertiary hospital

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Background: Prevention is the treatment of choice for drug allergy. However, many drugs can cause drug allergies, and clinical features such as symptoms, cross-reactive drug group/tolerable alternative drug group were somewhat different between patients who had allergies to the same drug. To date, drug safety card regarded to prevent drug allergy but have some limitations. we aimed to develop a smartphone-based drug allergy preventive system.

Method: The smartphone application called Smart-DUR is designed to operate based on the personal information of drug allergy including culprit drug, potentially cross-reactive drug group and tolerable similar-efficacy drug group. Smart-DUR app operated based on ATC (anatomical therapeutic chemical) code primarily and modified an ontology-based 2ndary database

Results: Smart-DUR app offered the mobile drug safety card with the additional action plan for their drug allergy. The patients could be checked on app whether a specific drug was dangerous to themselves or not. By scanning the QR or 2D bar-code on prescription paper, Smart-DUR app can detect a hazardous drug automatically. Smart-DUR app had the following additional features: (1) Distinct messages might be retrieved according to the patient's drug allergy information. In the patient's with aspirin/NSAIDs hypersensitivity, Smart-DUR app answered that all NSAIDs should be prohibited. However, in patients with diclofenac hypersensitivity, Smart-DUR app messaged that NSAIDs other than acetic acid derivatives (ATC code: M01AB) were tolerated. (2) Smart_DUR app can register multiple information for different drug allergies. (3) Based on the pre-specified database for combination drugs, Smart-DUR app can also review the safety of individual ingredients from combination drug. (4) Smart-DUR app can parallelly warn if the ingredients were included in culprit drug or cross-reactive drug group but had a different ATC code. Now, to test the feasibility of Smart-DUR app, we are conducting a pilot study with 100 patients with drug allergy from 4 tertiary hospitals.

Conclusion: We developed the smartphone-based drug allergy prevention systems. By using Smart DUR app, patients with drug allergy can easily prevent re-exposure to dangerous drugs.

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OA0149 | Relationship between new cases of anaphylaxis and use of beta-blockers: A systematic review and metaanalysis of observational studies

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Background: Beta-blockers (BBs) are key components of the pharmacologic treatment of ischemic heart disease. BBs can reduce mortality and re-infarction rates in patients after myocardial infarction. BBs have been associated with an increased risk of anaphylaxis, however, evidence supporting these observations is controversial. We carried out a systematic review and meta-analysis of studies that assess the influence of BB on new cases of anaphylaxis.

Method: We searched PubMed/MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Web of Science for relevant observational studies. We searched for studies where new cases of anaphylaxis were compared between patients taking BBs or not. The quality of evidence was assessed again using the recommendations of the GRADE guidelines. We performed a meta-analysis using a random-effects model.

Results: A total of 8 studies met the study criteria. The studies brought together 18,101 anaphylaxis episodes of new cases of anaphylaxis.

BBs did not increase the risk for new episodes of anaphylaxis (BBs, OR 1.40, 95% CI 0.91-2.14) in the pooled metaanalysis, the meta-analysis of cross-sectional studies and case-control studies, or the analysis with adjusted or non-adjusted ORs. Application of the GRADE scale for the influence of BB on new anaphylaxis episodes revealed the quality of evidence to be very low. It was not possible to perform an analysis adjusted for cardiovascular diseases, since only 1 study for BBs had adjusted data.

Conclusion: BBs did not increase the risk for new episodes of anaphylaxis in our study.

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CUTTING EDGE IMMUNOLOGY OF AIRWAY MUCOSA

OA0150 | Distinct microRNA expression patterns after IL-33 challenge in murine lung and bone marrow

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Background: Bone marrow (BM) type 2 innate lymphoid cells (ILC2s) have previously been identified to play key roles in IL-33-induced eosinophilic inflammation. However, the mechanisms regulating the properties of ILC2s in this model are unclear. MicroRNAs (miRNAs) are regulators of mRNA translation and have been involved in immune regulation of several diseases, such as allergy and asthma. In this study, we determined the miRNA expression patterns in BM and lung tissue samples from IL-33 challenged mice. We also focused on the regulation of BM derived ILC2s in response to IL-33 challenge and pathways involved in IL-33 driven inflammation.

Method: Wild type mice were challenged with recombinant IL-33 or PBS intranasally every other day for five days. BM and lung tissue were collected 24 h after the final challenge. RNA was isolated and microarray analysis was performed. A miRNA was determined to be differently expressed if the fold change was > 2 and *P*-value < .05. KEGG pathway analysis was performed using miRSystem. Distinct microRNAs expression profiles were validated by qPCR. The activity of the mTOR target ribosomal protein S6 (Rps6) in ILC2s from IL-33 challenged and PBS mice was measured by flow cytometry.

Results: In total 62 and 34 miRNAs were up-regulated in the IL-33 challenged group from the lung and BM, respectively. No miRNAs were found down-regulated in the lung whereas 129 miRNAs were down-regulated in the BM. MAPK and mTOR signaling pathways were identified as top candidates for the differentially expressed miRNAs in both lung and BM. Suggested mTOR regulators including miR-501, miR-142 and miR-150 were all validated by qPCR. The activity of the mTOR target Rps6 was increased in BM ILC2s from IL-33 challenged mice.

Conclusion: Our data suggest that miRNAs may have a regulatory role in IL-33-induced inflammation involving both mTOR- and MAPK-signaling pathways. Furthermore, mTOR signaling may be involved in IL-33-induced ILC2 driven BM eosinophilia. Several of the identified miRNAs have previously been proposed to be involved in the regulation of inflammatory processes. miR-150, which may act as a mTOR suppressor, could potentially be one miRNA explaining the increased activity of the mTOR target Rps6 in BM ILC2s. However, further studies need to be performed in order to determine the exact role of miRNA regulation in IL-33 inflammatory disorders, including asthma.

OA0151 | Deciphering human lung mast cell heterogeneity and Wnt signaling

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Background: Mast cells are strongly implicated in the pathogenesis of allergies and asthma. However, the role of different mast cell populations and mediators in the pathology of inflammatory airway diseases remain unclear. In this study, we hypothesized that there is a heterogeneity among human lung mast cells that play a pivotal role for the features of asthma and we aimed to characterize the heterogeneity in an unbiased way.

Method: We utilized a flow cytometry panel of 334 different markers (legendscreen) to determine if we on the protein level can identify and group the human lung mast cells into subpopulations.

Results: We identified several novel markers expressed on human lung mast cells (>20 previously not described), and several markers had a high degree of expression variability. Co-stainings of the markers with the highest expression variability revealed that six of these markers were co-expressed (SUSD2, CD34, CD49a, CD66, CD326 and HLA-DR), indicating that they separate human lung mast cell subtypes. Further investigation is needed to elucidate any functional differences of these cells. One family of novel receptors identified on human mast cells is the expression of Frizzled receptors. The agonists to the Frizzled receptors are Wnts and Wnt signaling is primarily involved in embryonic development, proliferation, differentiation and tissue damage/repair. Recent findings have implicated Wnt pathways in critically regulating inflammatory responses, especially in asthma. The role(s) of Wnt signaling in human mast cells is however unknown and to investigate this we treated human mast cell progenitor and mature mast cells with Wnts and examined proliferation, differentiation, activation and release of mediators. Our results show that Wnts do not affect human mast cell differentiation or proliferation, but Wnt-3a caused b-catenin stabilization in mature mast cells. Supernatants from mature mast cells screened on Olink proteomics inflammation panel, analyzing 92 inflammation-related proteins, indicated that a number of chemokines were released in response to Wnt-3a. The upregulation of IL-8 and CCL8 was confirmed by qPCR and the release of IL-8 by ELISA.

Conclusion: Our study demonstrates novel receptors on human lung mast cells, where the Frizzled receptors, induce chemokine release in mast cells. The results hold promises for further characterization of novel pathways for mast cells that might be of importance for their role in the pathogenesis of asthma and other respiratory diseases.

OA0152 | The nasal mucosa of local allergic rhinitis patients harbours IgE+ plasma cells

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Background: Local allergic rhinitis (LAR) is a well-defined rhinitis phenotype, but its pathophysiology remains unclear. In this study, we aim to investigate the involvement of IgE responses in LAR mechanisms.

Method: Allergic rhinitis (AR) patients (5), LAR individuals (9) and healthy non-atopic controls (5) were challenged for three days with house dust mite (HDM) extract, and nasal symptoms were recorded. Mucosal biopsies and peripheral blood specimens obtained before and after the nasal challenge were used for immunostaining *in situ*, cell culture/flow cytometry and basophil activation test (BAT). Nasal HDM-specific IgE (NsIgE) was also measured after the challenge.

Results: Both AR and LAR patients experienced typical allergic symptoms and significant increases in tissue eosinophils, whereas the controls did not. NsIgE was detected in 2/5 AR (40%) and 3/9 LAR (33%) patients and in none of the controls. BAT was positive in 5/5 (100%) of AR patients, in 3/8 (38%) of LAR individuals with reactive basophils, and in none of the controls. After the challenge, the number of mucosal IgE+FcεRI+cells was comparable between AR and LAR subjects, and significantly higher than in controls ($P < .001$ and $P < .005$, respectively). The number of mucosal IgE+CD38 + plasma cells (PC) after the challenge was also similar in AR and LAR patients, and significantly higher than in controls ($P < .05$ and $P < .01$, respectively). After the challenge, the proportion of HDM-stimulated peripheral inflammatory CD19 + CD20-CD138 + CXCR3 + IgE+PCs was comparable between AR and LAR patients, and significantly higher than in controls ($P < .01$ and $P < .05$, respectively). On the other hand, the proportion of HDM-stimulated peripheral CD19 + CD20 + CD27 + CD38 + IgE+plasmablast after the challenge was significantly higher in AR patients than in LAR ($P < .001$) and control ($P < .001$) individuals.

Conclusion: Our results indicate that IgE is produced in the mucosa of both AR and LAR patients. Moreover, a proportion of the IgE might be HDM-specific, as indicated by the BAT/NsIgE results. The larger proportion of peripheral IgE+plasmabast in AR patients might reflect a preferential systemic maturation process of IgE+PCs in AR patients, as compared with LAR individuals. Studies are ongoing to investigate whether class switch recombination to IgE occurs in the mucosa of LAR patients, as reported for AR individuals.

OA0153 | Proteomic analysis reveals the potential effects of exosomes on human nasal epithelial cells

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Background: Chronic rhinosinusitis (CRS) is an inflammatory disease whose mechanisms of pathogenesis are not fully elucidated. Exosomes are nanovesicles that have important biological functions. We sought to explore the roles of epithelial derived-exosomal proteome obtained from the healthy and diseased human nasal epithelium in modulating CRS.

Method: We sampled exosomes from nasal lavage fluid and primary human nasal epithelial cells (hNECs) from healthy controls, patients with CRS and patients with asthma and co-existing CRS. The presence of exosomes was confirmed using Nanosight assay, transmission electron microscopy and western blotting. Exosomal proteome was profiled with mass spectrometry. Cell Counting Kit-8 kit was applied to confirm the roles of exosomes on mediating cellular proliferation.

Results: Exosomes can be detected in both nasal lavage fluid and the supernatant of hNECs among the three groups. The hNEC-derived exosomes from diseased epithelium contained differentially expressed proteins that are mainly involve in epithelial remodeling via the extracellular matrix-receptor interaction, p53, PPAR, PI3K-AKT and focal adhesion pathways. I*n vitro* functional study of the exosomes further demonstrated that epithelial-derived cellular exosomes from patients with CRS and asthmatic patients with CRS significantly reduced the rate of proliferation of normal hNECs with effective concentration of ≥ 10 μg/ml.

Conclusion: Exosomes secreted by hNECs from patients with CRS, regardless of co-existence of asthma, are laden with proteins that influence cell proliferation and tight junction pathways potentially leading to remodeling of the sinonasal mucosa.

OA0154 | Temporal profiling of type 2 airway inflammation markers in nasal mucosal lining fluid following a grass allergen challenge

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Background: Pollen-allergic rhinitis is driven by the cellular release of inflammatory mediators upon pollen exposure. Nasal challenge with pollen extracts is a research tool to understand the local, cellular events triggering allergic airway inflammation, where measurement of inflammatory mediator release following a nasal challenge may reveal the molecular mechanisms of allergic airway inflammation.

Method: A nasal challenge was performed by spraying 100 μl of grass allergen extract into both nostrils of one individual. Temporal profiles

of inflammatory mediators were then investigated using Nasosorption, which allows for minimally-invasive serial respiratory sampling, in combination with several novel immunoassays to capture early (0-120 min) and late (120-480 min) phase airway inflammation post allergen exposure. Nasal fluid was subsequently eluted into 300 µl elution buffer and analyzed using immunoassays for tryptase, eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), myeloperoxidase (MPO), neutrophil gelatinase-associated lipocalin (NGAL), sIgE-g6, and cytokines IL-5, IL-13, eotaxin, IL-6 and IL-8.

Results: All analytes, except IgE to grass, increased during the early (tryptase) or late phase (EDN, ECP, MPO, N-GAL, and cytokines). Some of the measured proteins, e.g. EDN and IL-5, increased dramatically by several hundred fold and temporal profiles of EDN and ECP coincided with IL-5 and IL-13.

Conclusion: Previous studies have shown that there is an increase in the numbers of inflammatory cells in the nasal mucosa during pollen season and that this is correlated with the severity of rhinitis symptoms. Our results from the nasal challenge and measurement of cell-specific inflammatory markers agree with this, particularly that the kinetics of eosinophil (e.g. EDN and ECP) and Th2 (e.g. IL-5 and IL-13) related cytokines are closely related. However, further studies on additional individuals are needed to determine the variation between individuals, and the variability of the sampling procedure. Conceivably, a combination of a nasal sampling device and type 2 airway inflammation biomarkers may have the potential to serve as a diagnostic tool in nasal challenges, allowing for the determination of individual endotypes of allergic rhinitis patients.

OA0155 | Repeated exposure to house dust mite drives persistent activation of inflammatory macrophages

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Background: Airway macrophages are critical to pulmonary immunity and maintenance of lung function as they produce a wide array of pro-inflammatory cytokines and eicosanoids. Thus, aberrant or chronic macrophage activation can contribute to inflammatory diseases. Repeated exposure to microbes evokes an "innate memory", resulting in stronger responses or tolerance upon secondary exposure. Whether repeated contact to allergens persistently alters macrophage cytokine and eicosanoid profiles and how this impacts allergic inflammation remains unknown.

Method: Alveolar-like monocyte-derived macrophages (aMDM) were differentiated from $CD14^+$ monocytes of healthy human volunteers. Cells were "trained" with house dust mite (HDM) for 24 h before washout and re-stimulation a week later. Culture supernatants after initial, and before and after secondary exposure were analyzed by LC-MS/MS and multiplex cytokine assays. Proteins were quantified via western blot.

Results: Training of aMDM with HDM resulted in an activated cell morphology and secretion of pro-inflammatory cytokines (IL-1β, IL-6, IL-10, TNFα) 24 h after training, which mostly returned to baseline levels after 6 days. In contrast, CCL17 was initially induced by HDM and further increased with time (until day 13). Similarly, CXCL10 and microsomal prostaglandin E2 synthase (mPGES1) remained elevated in HDM-trained aMDM for 7 days. Treatment with a histone deacetylase inhibitor during training decreased PGE_2 production of trained aMDM after 7 days. After re-exposure to HDM, trained aMDM produced more eicosanoids (PGE_2, TXB_2, LTB_4 and 12-HETE) than acutely exposed aMDM.

Conclusion: HDM training of differentiated macrophages profoundly and persistently changed cytokine production. The increased capacity to produce CCL17 could increase influx of T_H2 cells into the lung leading to increased allergic inflammation. Augmented inflammatory cytokine responses and epigenetic modifications causing an altered PGE_2/LTB_4 ratio upon HDM re-exposure could perpetuate ongoing type 2 inflammation. Thus, targeting allergen-driven macrophage reprogramming could lead to new therapeutic options for allergic diseases.

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ENVIRONMENTAL FACTORS INFLUENCING ALLERGIC RESPONSES

OA0156 | Transfer and loss of allergen-specific responses via hematopoietic stem cell transplantation in children: A prospective observational study

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Background: Transfer of IgE-mediated allergies via hematopoietic stem cell transplantation (HSCT) has been described in case reports and small series. Unselected, prospective studies investigating the probability of transferring, losing or *de novo* acquisition of allergic sensitization after HSCT have been lacking. Understanding this process is key to allow relevant risk assessment by blood services and affect the clinical management in the context of HSCT.

Method: In this observational study, 50 donor-recipient pairs undergoing first HSCT were prospectively enrolled to assess the risks of transferring allergen-specific IgE responses from the donor to the recipient and of abolishing established allergen-specific responses in the recipient via HSCT. Allergen-specific IgE and IgG to 156 allergens were measured in donors and recipients pre-HSCT and in recipients 6, 12 and 24 months post-HSCT by allergen microarray and detailed interviews were performed, assessing the atopic history in recipients and their families. Based on a mixed effects model we determined risks-estimations of transfer or maintenance of allergen-specific IgE- or IgG responses two years post-HSCT.

Results: Pre-HSCT, 22 recipients displayed a total of 146 different allergen-specific IgE responses. Post-HSCT, 94% of allergen-specific IgE responses were lost. Two years post-HSCT, recipients' allergen-specific IgE was significantly linked to the pre-HSCT donor or recipient status. The estimated risk of maintaining and transferring individual IgE responses to allergens by HSCT was 1.7% (0.000-0.37, 95% prediction interval) or 2.3% (<0.001-0.50, 95% prediction interval), respectively. Allergen-specific IgG, which served as a surrogate marker of maintaining protective IgG responses, was highly associated with the donor's (31.6%) or the recipient's (28%) pre-HSCT response.

Conclusion: Allergen-specific IgEs are profoundly decreased in recipients post-HSCT. However, there is a considerable risk of transfer from the donor. These findings need to be implemented in the clinical management of HSCT to improve safety and quality of life of affected patients.

OA0157 | Synergistic suppression: Transport of quercetin-iron complexes by beta-lactoglobulin results in immune tolerance due to increased labile iron and activation of the aryl hydrocarbon receptor

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Background: The lipocalin beta-lactoglobulin (BLG) is a known cow milk allergen, which is perplexingly also protective against allergy when consumed in raw farm milk. Lipocalins act as innate defense proteins with physiological cargo function. Previously, we reported that *in vitro* only ligand-loaded holo-lipocalins prevented Th2-immune responses in immune cells. We assessed *in vivo* the immune response to ligand-free (apo) versus iron-quercetin complexes loaded (holo) BLG using a BALB/c mouse model and addressed the molecular mechanism *in vitro*.

Method: The flavonoid quercetin, forming strong complexes with iron, was used as a model ligand. Complex-formation of iron-quercetin and binding into BLG was controlled by spectroscopy and calculated *in silico*. Mice were nasally treated biweekly (6x) with apoBLG, holoBLG loaded with iron-quercetin complexes, or controls (deferoxamine or iron-quercetin complexes alone). Nasally treated mice were challenged with BLG on the day of sacrifice, and their body temperature monitored. Lungs were assessed for Cyp1A1, a downstream target of the aryl hydrocarbon receptor (AhR), splenocytes were evaluated by FACS, specific antibodies, and cytokines by ELISA. Peripheral blood mononuclear cells for intracellular iron. Activation of the AhR was measured using the reporter cell line AZ-AHR.

Results: Exposure to holoBLG did neither induce specific IgE or IgG formation, nor anaphylaxis, but promoted regulatory T cells and Cyp1A1 expression *in situ*. BLG facilitated the quercetin-dependent activation of the AhR-pathway and increased intracellular iron in monocytic cells.

Conclusion: The cargo of holoBLG is decisive in avoiding allergic sensitization *in vivo*. HoloBLG activates the AhR and elevates the intracellular labile iron, both providing a strong anti-inflammatory signal and promoting tolerance. HoloBLG may participate in the allergy- and asthma protective effect of farm milk.

OA0158 | Loading of beta-lactoglobulin confers cross-protection against sensitization to the major birch pollen allergen Bet V 1 in a BALB/c mouse model

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Background: In our previous studies, we proved that the unloaded apo-form of the lipocalin beta-lactoglobulin (BLG) promoted Th2 cells and inflammation, whereas the loaded, holo-form acted rather in a tolerogenic manner. Here we tested in BALB/c mice whether nasal application of holo-BLG prevented the onset of allergy (i) to BLG or (ii) to an unrelated allergen such as the major birch pollen allergen Bet v 1.

Method: BALB/c mice were nasally treated 4 times in biweekly intervals with the unloaded apo-form of BLG, or holo-BLG with quercetin-iron complexes as ligands, or water as sham-treatment, before sensitizing mice twice intraperitoneally with apo-BLG or apo-Bet v 1 in conjunction with aluminium hydroxide. Subsequently, body temperature drop was recorded using the anaphylaxis imaging cage. Specific antibodies in serum as well as cytokines of BLG- and Bet v 1-stimulated splenocytes were analyzed by ELISA.

Results: Allergic sensitization to BLG, and to Bet v 1 could only be prevented when mice were pre-exposed to holo-BLG. Mice pretreated with holo-BLG had significantly lower BLG– or Bet v 1–specific antibodies (IgG1, IgG2a, IgA and IgE) than apo-BLG or sham-treated animals. The level of Th2-type BLG-specific cytokines (IL5, IL13 and IL10) was significantly reduced in the group pre-treated with holo-BLG and then sensitized with BLG. Sensitization to Bet v 1 led to similar Bet v 1-specific cytokine responses (IL5, IL13, IL10 and IFNγ) in the different pre-treated groups. Nevertheless, pre-treatment with holo-, but not apo-BLG prevented clinical reactivity and body temperature drop upon allergen-challenge with either apo-BLG or apo-Bet v 1.

Conclusion: Prophylactic treatment with holo-BLG prevented the onset of allergy to BLG as well as to a non-related allergen. This supports that holo-BLG exploits innate immune suppressive mechanisms addressed in a parallel study.

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OA0159 | Antibody conjugates Bi-specific for allergens and ICAM1 prevent epithelial allergen penetration and rhinovirus infection

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Background: Recently it has been demonstrated that passively administrated human monoclonal allergen-specific IgG antibodies significantly reduce allergic symptoms in allergic patients. However, the efficacy of systemic antibody-based treatment depends on the ability of antibodies to block patients' IgE binding to the allergen. To develop a non-invasive topical form of treatment with the aim to prevent the penetration of allergens through the respiratory epithelial barrier, we hypothesized that such a treatment can be performed even with an allergen-specific IgG antibody which does not inhibit allergic patients' IgE binding to the allergen.

Method: Antibody conjugates bi-specific for the major grass pollen allergen Phl p 5 and ICAM1, a major group rhinovirus receptor on respiratory epithelial cells, were generated by coupling a Phl p 5-specific, IgE non-blocking antibody and a monoclonal ICAM1-specific antibody. Anchoring of allergens on the surface of the human bronchial epithelial cell line 16HBE14o- by these conjugates was investigated by immunofluorescence microscopy. The ability of the conjugates to inhibit transepithelial allergen migration through 16HBE14o- cell monolayers and basophil degranulation underneath was examined by transwell migration assays and basophil activation tests, respectively. The capacity of the conjugates to prevent rhinovirus infection of 16HBE14o- or HeLa cell monolayers was analyzed by impedance-based xCELLigence Real Time Cell Analysis system and rhinovirus neutralization assays.

Results: The engineered bi-specific antibody conjugates immobilized Phl p 5 on the surface of epithelial cells, significantly reduced allergen penetration and decreased allergen-induced basophil activation. In addition, antibody conjugates prevented rhinovirus infection of 16HBE14o- and HeLa cells.

Conclusion: Our study shows that antibody conjugates consisting of a single allergen-specific, IgE non-blocking antibody and an ICAM1-specific antibody prevent allergen penetration through respiratory epithelium and allergic inflammation as well as rhinovirus infections and may be used for treatment of allergen and rhinovirus-induced respiratory diseases. Supported by FWF grants F4607, F4613, F4605, F4611, P29398.

OA0160 | The effect of triclosan exposure on the development of allergic diseases

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Background: Little is known about the effect of triclosan on the development of allergic diseases in children. This study investigated the associations (i) between triclosan exposure and allergic diseases in children; (ii) between triclosan exposure and sensitization markers for the possible disease pathogenesis; and (iii) gender-based differences.

Method: A total of 453 children from the Childhood Environment and Allergic diseases Study (CEAS) cohort with urine samples were recruited. Urine triclosan levels were measured by UPLC-MS/MS and markers of sensitization (IgE) were measured by ELISA at the age 3 and 6. Information on serum IgE levels and the development of allergic diseases was collected. The association between triclosan levels at different stages and IgE levels, and allergic diseases were evaluated by multivariate linear regression and logistic regression.

Results: The triclosan levels at age 3 were higher than those at age 6 (geometric mean 1.05 vs 0.37 ng/mL). Triclosan levels at age 3 positively correlated with serum IgE levels at age 3 and 6 (per ln-unit: β=44.561 KU/l, P = .002; per ln-unit: β=75.761 KU/l, P < .045). Interestingly, analyses stratified by gender revealed that triclosan levels positively correlated with IgE levels at age 6 were only shown in boys (per ln-unit: β=78.94, P = .013). Asthma and atopic dermatitis at age 3 were significantly associated with triclosan (adjusted OR 1.14, 95%CI 1.01-1.29; adjusted OR 1.22, 95%CI 1.05-1.41). Analyses stratified by gender revealed that triclosan levels were significantly associated with asthma, AR, and AD only in boys.

Conclusion: Exposure to triclosan at young age was associated with IgE levels and may increase the risk of the development of atopic disorders in children.

			Age 3 Ln-triclosan	
Asthma Adjusted OR (95% CI)[a]	Age 3		1.00	1.14 (1.01-1.29)*
		Boys	1.00	1.25 (1.07-1.47)*
		Girls	1.00	0.95 (0.76-1.19)
Asthma Adjusted OR (95% CI)[a]	Age 6		1.00	0.94 (0.79-1.11)
		Boys	1.00	1.04 (0.85-1.28)
		Girls	1.00	0.68 (0.45-1.04)
Allergic rhinitis Adjusted OR (95% CI)[a]	Age 3		1.00	1.12 (0.99-1.26)
		Boys	1.00	1.18 (1.02-1.37)*
		Girls	1.00	0.99 (0.80-1.23)
Allergic rhinitis Adjusted OR (95% CI)[a]	Age 6		1.00	1.01 (0.86-1.20)
		Boys	1.00	1.14 (0.91-1.42)
		Girls	1.00	0.80 (0.56-1.14)
Atopic dermatitis Adjusted OR (95% CI)[a]	Age 3		1.00	1.22 (1.05-1.41)*
		Boys	1.00	1.25 (1.04-1.50)*
		Girls	1.00	1.15 (0.89-1.48)
Atopic dermatitis Adjusted OR (95% CI)[a]	Age 6		1.00	1.00 (0.83-1.21)
		Boys	1.00	1.07 (0.86-1.33)
		Girls	1.00	0.82 (0.54-1.25)

OR, odds ratio; CI, confidence interval.
*P < .05.
[a]Adjusted for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure.

OA0161 | Prevalence and predictive factors of pollen food syndrome in a canadian cohort of birch, grass and/or ragweed allergic individuals

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Background: Pollen food syndrome (PFS) is an IgE-mediated food allergy that occurs in aeroallergen sensitized individuals, due to cross-reactivity of plant proteins with homologous proteins present in food. In Northern/Central Europe and North America, culprit aeroallergens include: birch, grass and ragweed. Few prognostic factors for PFS have been identified, and there is limited data on the epidemiology of this condition in Canada.

Method: A retrospective chart review was completed of patients seen in a single Canadian allergy clinic in Kingston, ON, Canada. Adult patients with allergic rhinitis and sensitization to birch, grass and/or ragweed pollen, based on positive skin prick testing, who were seen between 2009-2018, were included in our study. Patients were considered to have PFS based on physician diagnosis. Variables of interest including: symptom severity, and multiple aeroallergen sensitization were assessed with a Pearson's chi-square test. The relationship

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between skin prick test size of aeroallergens of interest and the presence of PFS was assessed using a binomial logistic regression.

Results: Of 225 patients identified with sensitization to an aeroallergen of interest, 50 (22.2%) had a concomitant physician diagnosis of PFS. PFS occurred significantly more frequently in those patients with increased symptom severity (P = .02), multiple aeroallergen sensitization (P = .00001) and birch and alder sensitization, compared to birch sensitization alone (P = .02). Larger skin prick test size to birch was associated with the presence of PFS (OR = 1.10; 95% CI, 1.04-1.18).

Conclusion: Our preliminary data, similarly to previous studies, suggests that increased rhinitis severity and multiple aeroallergen sensitization are associated with PFS. Additionally, birch and alder co-sensitization were associated with higher rates of PFS than birch sensitization alone, and larger skin prick test size to birch was correlated with PFS. In our Canadian cohort of patients, the rate of PFS was 22.2%.

TUESDAY, 4 JUNE 2019

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ACHIEVING TOLERANCE AND BETTER QUALITY OF LIFE IN FOOD ALLERGIC PATIENTS

OA0162 | Maternal anxiety correlates with infant skin prick test size and inhibits cow's milk tolerance induction in their infants

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Background: Maternal anxiety before and during pregnancy has been associated with higher rates of atopy in children. We measured maternal anxiety prospectively in a randomised, controlled trial of low dose introduction of baked milk products in newly diagnosed cow's milk allergic infants.

Method: Inclusion criteria were age < 12 months, a physician-diagnosed CM allergic reaction < 2 months before assessment and a positive skin prick test (SPT) to milk +/- raised splgE to milk. FAQL-PF, the Food Allergy Independent Measure (FAIM) and the State (acute, transient)/Trait (long term/permanent) Anxiety Inventory (STAI) questionnaires were completed by mothers before the single dose OFC of the ED_{05} for CM (0.5 mg milk protein) or no dose. All infants were to introduce baked milk at home using the 12-step MAP milk ladder.

Results: 15 children recruited to date have been followed to 6 months. SPT to milk at baseline was significantly negatively associated with milk ladder position (MLP)at both 3 m (Spearman's r = −.63, *P* = .004) and 6 m (r = −.78, *P* = .007). Multiple Linear Regression (MLR) showed a strong positive association between milk SPT at recruitment and maternal Trait anxiety (B = 0.85, *P* = .49; 95% C.I. = 0.04, 8.9) but not maternal State anxiety. Maternal state (M = 38.4, SD10.7, B = −0.16, 95% C.I. = −0.18, −0.13; *P* = .01;) and Trait anxiety (M = 40.8, SD 8.9, B = −0.04, 95% C.I. = −0.06, −0.02; *P* = .03) at recruitment were strongly negatively associated with MLP at 6 m. FAIM (M = 4.4,SD1.1) but not FAQLQ, was significantly associated with MLP (B = 11.8, 95%C.I. = 8.5-15.0,*P* = .01) and with State anxiety (B = 1.8, 95% C.I. = 1.3-2.3,*P* = .01).

Conclusion: Mothers with anxious personalities have allergic children. This study shows for the first time that maternal anxiety is directly associated with levels of IgE sensitisation in cow's milk allergic infants and, more importantly, that this long-term maternal anxiety profile/personality trait, which predates their child's allergic diagnosis, strongly affects how quickly tolerance to milk can be achieved, using established methods of active tolerance induction.

OA0163 | Does introduction of baked milk products increase tolerance to milk proteins in milk-allergic children?

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Background: Allergy to cow milk (CM) is one of the common food allergies in childhood. The ability to tolerate baked milk (BM) has been associated with an increased probability of developing tolerance to raw milk.

Method: Prospective historical cohort study that compared children (0-4 years old at first symptoms) with IgE-mediated CM allergy that strictly avoided CM proteins in the diet with patients who tolerated or introduced BM products. Patients were included in 3 groups: A, strictly avoided CM protein; B, always contacted with BM; C, initiated BM after negative food challenge or BM introduction at home. Immunologic parameters were measured and used for comparison between groups to evaluate the natural history of tolerance development.

Results: The study included 101 children (40 females, 61 males). Anaphylaxis occurred in 29 patients. The median age at first symptoms was 4 months, and the median sIgE to CM at diagnosis was 8.55 kU/L. Sensitization to casein occurred in 57 patients and sIgE to casein was 20.01 kU/L (SD 27.40). Sixty-nine patients maintained strict eviction of CM (group A), 5 patients tolerated BM at enrollment and maintained ingestion (group B) and 27 patients introduced BM after some period of strict eviction (group C). Spontaneous tolerance to raw CM (defined by negative oral food challenge or asymptomatic accidental ingestion without oral immunotherapy) occurred in 35 patients (26/69 eviction group vs 9/32 BM tolerant group, NS) and no significant differences were observed in the time to tolerance between the groups.

Patients that achieved tolerance had, at the time of diagnosis, lower sIgE to CM (28.07 vs 8.77, *P* = .015) and sIgE casein (23.24 vs 3.55, *P* < .001) [S3] and smaller prick test wheals to CM (7.32 vs 4.41, *P* = .014)[S4] . Age of allergy onset did not associate with development to tolerance.

Conclusion: In our study, ingestion of BM did not increase the probability or the speed of spontaneous tolerance acquisition to raw CM but it showed no deleterious effect and might allow a less strict diet. Lower sIgE and smaller prick test at the diagnosis are good predictors of spontaneous tolerance development.

OA0164 | Spanish children with acute FPIES usually tolerate all other food groups

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Background: Acute FPIES triggered by multiple unrelated foods ("multiple foods FPIES") has been reported in 35-65% of US series [1,2]. This has led to complex weaning recommendations in children with FPIES [3]. However, evidence suggests that multiple food FPIES is rare in Southern Europe [4], which questions the applicability of such weaning advice in this population. Studies including a detailed dietary history in children with FPIES are lacking.

Method: To describe the prevalence of multiple food FPIES and other food allergies in a cohort of Spanish children with acute FPIES. Methods: Characteristics of children (0-18 years) taking part in the BIO-FPIES multicentre study was assessed. All children met diagnostic criteria for acute FPIES to at least one food [5,6]. Detailed dietary history was taken at screening for all food groups (cow's milk, egg, soya, wheat/gluten, rice, corn, vegetables, fruits, meat/poultry, fish, shellfish, nuts, seeds, legumes). For each food group, children were classified as "tolerant," "not exposed," "sensitised but not exposed," "acute FPIES," "IgE allergy" or "non-FPIES, non-IgE allergy."

Results: Of 83 eligible children, 10 were excluded due to incomplete dietary history, leaving 73 children for analysis. Mean age at onset of FPIES was 1.2 years (range: 0-18). Mean age at inclusion was 4.1 years (Range: 1.2-18). The culprit foods triggering the index FPIES reaction were: fish (45, 61.6%), egg (12, 16.4%), milk (11, 15%), rice (2, 2.7%), shellfish, chicken and mushroom (1, 1.4% each). Most children (62/73, 85%) had FPIES to a single food/food group with no evidence of other food allergies and most of them had tried all other groups of foods. Only 4 children had FPIES to multiple unrelated food groups (2 children to fish and shellfish, 1 child to chicken, turkey and potato, 1 child to fish, rabbit and pumpkin). Seven children had food allergies other than FPIES to a variety of foods.

Conclusion: Up to 85% of children with acute FPIES from Spain tolerate all other food groups. A minority of patients develop acute FPIES to multiple foods (5%) or food allergies other than FPIES (10%). In those with multiple food groups/allergies involved, there is great heterogeneity regarding culprit foods and underlying mechanisms. It is not currently possible to predict which foods may cause additional reactions when weaning such children with FPIES. Unrestricted weaning advice seems appropriate for most Spanish children with acute FPIES.

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OA0165 | Validation of food allergy quality of life short forms (FAQLQ-10) for parents, children and teens

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Background: Health-related quality of life (HRQL) is rarely evaluated in clinical contexts due to time and resource constraints. We created brief versions of the Food Allergy Quality of Life Questionnaires (FAQLQ) for use in research and clinical contexts, to reduce the time burden on respondents and facilitate self-reporting by younger allergic patients, and then used them to assess changes in HRQL following DBPCFC in peanut-allergic young people and their parents.

Method: In Phase 1, pre-existing datasets from Cork University Hospital and Sechenov Moscow were used to develop 10-item proxy (0-12 years), and self-report (0-12; 13-18 years). In Phase 2, short forms were completed (baseline/6 months) by participants and their parents undergoing DBPCFC in the BOPI Study, a Phase 2b/3 randomized controlled trial assessing oral peanut immunotherapy (Clinicaltrials.gov NCT02149719). Reliability and criterion validity were assessed by Cronbach's alpha and Pearson coefficients. ANOVAs examined discriminant validity, and change from baseline to 6 months.

Results: Twenty-one children (0-12 years), 35 teens (13-18 years) and 56 parents completed FAQLQ and Food Allergy Independent Measure

(FAIM).Very high internal reliability was found for all forms (>0.85). Significant correlations between FAIM and all FAQLQ measures ($P < .05$), and significant differences based on history of anaphylaxis (MD = 1.1, SD 0.4, $P < .05$) demonstrated validity. Improvement in HRQL was found following DBPCFC, with those who experienced anaphylaxis at challenge reporting the greatest improved [MD 0.6 F = 6.688, $P = .01$]. Change score exceeded MID and was not associated with baseline score, demonstrating treatment effect is independent.

Conclusion: Preliminary analysis shows the new FAQLQ-10 are quick and easy to use precision instruments. HRQL improved across all age groups following DBPCFC, with greatest impact on those experiencing respiratory anaphylaxis. Improvement in DBPCFC may therefore be a confounding factor when assessing change in HRQL following food allergy desensitisation treatment.

OA0166 | Improvement in disease-specific quality of life for peanut-allergic subjects receiving AR101 maintenance therapy

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Background: Peanut allergy (PA) is one of the most common and persistent food allergies and is associated with poor health-related quality of life. There are currently no approved treatment options for PA. AR101 is an investigational oral biologic drug for use in oral immunotherapy in subjects with PA. PALISADE was a phase 3 double-blind, placebo-controlled trial that investigated the safety and efficacy of AR101 in subjects with PA. A subgroup of subjects continued daily AR101 maintenance therapy in an open-label extension (OLE) for 6 months. Here we report on the changes in the quality of life (QOL) in these subjects and in their parents/caregivers.

Method: Subjects aged 8 to 17 years (self-report) and parents/caregivers of subjects aged 4 to 17 years (proxy-report) completed an age-appropriate Food Allergy Quality of Life Questionnaire (FAQLQ) at screening and after OLE. Total scores were calculated for both time points and change was evaluated by Wilcoxon signed-rank tests using SAS version 9.4.

Results: At screening, the mean years since PA diagnosis were 8.1 and 67.3% subjects were reported to have experienced ≥ 1 anaphylactic reaction in their lifetime. 110 PALISADE subjects aged 4-17 years entered the OLE: 62.7% were aged 4-11 years and 37.3% aged 12-17 years; 52.7% were male; 79.1% were Caucasian and 93.6% completed. 68 subjects (self-report) and 93 parents/caregivers (proxy-report) completed the FAQLQ at OLE end. Statistically significant improvements were seen for self-report FAQLQ on all domains (Allergy Avoidance and Dietary Restrictions, Risk of Accidental Exposure, Emotional Impact) and on Total Score (all $P < .01$). Improvements were found for two of the three proxy-report FAQLQ domains and Total score (Social and Dietary Limitations: $P < .01$; Food Anxiety: $P < .05$; Emotional Impact: $P = .07$; Total score: $P < .01$). All mean self-reported FAQLQ score improvements exceeded the Minimal Important Difference of 0.5 (MID) as indicated by instrument developers.

Conclusion: PA subjects receiving daily AR101 during PALISADE and for 6 additional months in an OLE reported important and statistically significant improvements in disease-specific QOL. PA treatment with AR101 was shown to be associated with improved QOL in PA subjects.

OA0167 | A comparison between the quality of life of children undergoing oral immunotherapy for food allergy and the quality of life depicted by their parents

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Background: Quality of life (QoL) of food-allergic children, as measured by their parents, improves following oral immunotherapy (OIT). However, studies of children's QOL using questionnaires directed at the children themselves are lacking.

Method: The Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF) and the Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF) were translated to Hebrew and validated. The questionnaires were filled by parents and their 8- to 12-year-old children, undergoing OIT for food allergy at Assaf Harofeh Medical Center, at the beginning of treatment and upon reaching maintenance. Parental and child questionnaires were compared.

Results: 74 children aged 8-12 years undergoing OIT for milk, peanut, egg, sesame or tree-nut allergy, filled out the FAQLQ-CF and their parents filled out the FAQLQ-PF. Parent and child questionnaires were strongly correlated both at the start ($r = .488$, $P < .001$) and at the end ($r = .414$, $P < .001$) of OIT. However, the median (and interquartile range) total QoL score of the children at the beginning of treatment was significantly higher (worse) when assessed by themselves (4.85, 3.7-5.8) compared to how it was perceived by their parents (4.0, 3.2-5.12), ($P < .001$). Both the total FAQLQ-CF and the FAQLQ-PF scores improved significantly by the end of OIT (3.9, 2.85-5.2 and 2.95, 2.15-4.6, respectively) ($P = .001$), but a significant difference between parental and child questionnaires was still noted ($P < .001$).

Conclusion: While children with food allergy experience a significant improvement in QOL following OIT, they perceive their QOL as worse compared to their parents both before and after treatment.

TUESDAY, 4 JUNE 2019
OAS 29
FOOD ALLERGY AND EOSINOPHILIC ESOPHAGITIS

OA0168 | Basophil and mast cell responses to food allergens in sensitised but tolerant patients are not mediated via the FcgRIIa and FcgRIIb receptors

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Background: Allergen-specific IgE (sIgE) bound to FcεRI receptor expressed on basophils and mast cells is essential for the induction of an allergic response to food allergens. However, the presence of sIgE alone is not a reliable biomarker of food allergy, as most individuals with detectable sIgE in serum do not react on oral food challenge. Allergen-specific IgG antibodies may be implicated in the inhibition of basophil and mast cell responses to food allergens in sensitised tolerant individuals. The objective of this work was to investigate the role of IgG and their receptors in basophil and mast cell responses to food allergens.

Method: Children being assessed for peanut, egg or milk allergies were studied and grouped into allergic, sensitised but tolerant and non-sensitised non-allergic. Allergen-specific IgG1, IgG2, IgG3 and IgG4 levels in plasma were measured by ELISA. Whole blood basophil activation tests (BAT) to egg, cow's milk and peanut and mast cell activation tests (MAT) to peanut were performed with and without blocking antibodies against anti-FcγRIIα or anti-FcγRIIβ. Surface-bound IgE, IgA and IgG were measured on basophils and LAD2 cells. Surface receptors FcεRI, FcγRI, FcγRII, FcγRIIα, FcγRIIβ and FcγRIII were also quantified by flow cytometry.

Results: PA individuals showed higher levels of peanut-specific IgG1 ($P = .0056$), IgG2 ($P = .0027$) and IgG4 ($P = .0054$) as measured by ELISA compared to PS individuals. Basophils and LAD2 cells (following sensitisation with plasma) expressed high levels of IgE (78.34%/98.1%) and virtually no IgG (0.5%/0.35%) on their surface. Basophils and LAD2 cells expressed high levels of FcεRI (98.8%/99.3%) and low levels of FcγRI (mean basophils/mast cells = 3.82%/17.45%) and FcγRIII (3.59%/4.94%). Basophils expressed FcγRIIβ at higher levels than FcγRIIα ($P < .001$); conversely, LAD2 cells expressed greater levels of FcγRIIα than FcγRIIβ ($P < .001$). No differences were observed in FcγRIIα ($P = .7$) or FcγRIIβ ($P = .12$) expression on basophils between allergic and sensitised but tolerant individuals. Blocking FcγRIIα or FcγRIIβ in BAT experiments to egg, milk or peanut and in MAT experiments to peanut did not alter CD63 expression on basophils in response to allergen stimulation.

Conclusion: We found no evidence that FcγRIIα or FcγRIIβ contribute towards tolerant responses to food allergens in human BAT or MAT in vitro models. The role of IgG in modulating allergic responses is more likely mediated through an extracellular blocking mechanism.

OA0169 | Subclinical esophageal eosinophilia is present in some peanut allergic patients

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Background: Food allergies affect 1 in 13 children. Current practice is avoidance of culprit foods; however, oral immunotherapy (OIT) is an emerging treatment for food allergy. Despite attempts to minimize adverse events during the desensitization process, many participants still experience gastrointestinal symptoms and some develop eosinophilic esophagitis. The incidence of subclinical esophageal eosinophilia (EE) in food allergic patients at baseline is unclear. We evaluated the presence of EE in subjects with food allergy before and during peanut OIT.

Method: Baseline esophagogastroduodenoscopies (EGD) were conducted with 21 adults prior to enrollment in a peanut OIT clinical trial. Endoscopic findings were assessed using a standardized scoring system, the Eosinophilic Esophagitis (EoE) Endoscopic Reference Score (EREFS), and three biopsies were obtained from the proximal, middle, and distal esophagus. Esophageal biopsies were evaluated using the EoE Histologic Scoring System (EoEHSS). Hematoxylin and eosin stains of each biopsy were assessed for eosinophil density.

Results: All subjects were asymptomatic at enrollment. Pre-existing esophageal eosinophilia was present in 5 participants (24%), 3 (14%) of whom had > 15 eosinophils per high-power field (eos/hpf) associated with mild endoscopic findings (edema, linear furrowing, or rings; median EREFS = 0, IQR 0-0.25). Some subjects also demonstrated basal cell hyperplasia, dilated intercellular spaces, and lamina propria fibrosis of the esophageal mucosa.

Conclusion: Esophageal eosinophilia is present in adults with IgE-mediated peanut allergy prior to initiation of OIT. Eosinophilic inflammation in these subjects may be accompanied by mild endoscopic and histologic findings. Additional EGD and biopsies for longitudinal data collection during OIT is ongoing and may add insight into mechanisms behind gastrointestinal side effects. Further studies would be warranted to determine whether these findings are also present in children.

OA0170 | Efficacy of RPC4046, an anti-interleukin-13 monoclonal antibody, in patients with active eosinophilic esophagitis: Analysis of the steroid-refractory subgroup from the heroes study

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Background: The HEROES study evaluated RPC4046 in adults with active eosinophilic esophagitis (EoE). We conducted pre-specified and post-hoc analyses to assess RPC4046 in steroid-refractory subjects.

Method: Adults with EoE (n = 99) were stratified by steroid-refractory status (determined by prior corticosteroid use and investigator judgment) and randomized 1:1:1 to RPC4046 360 mg (n = 17), 180 mg (n = 14), or placebo (n = 16) weekly for 16 weeks. The primary endpoint was changed from baseline in mean esophageal eosinophil counts at week 16. Secondary endpoints included mean change from baseline to week 16 in EoE Endoscopic Reference Score (EREFS), improvements in dysphagia (Daily Symptom Diary [DSD]), Eosinophilic Esophagitis Activity Index (EEsAI) score, and EoE histology scoring system (EoEHSS) per grade and stage.

Results: At week 16, compared with placebo, each dose group showed significant improvements in mean esophageal eosinophil counts ($P \leq .0001$), EREFS ($P < .005$), and histology (EoEHSS) ($P < .05$), and a significantly greater proportion of patients had peak eosinophil counts < 15 per high-power field ($P < .01$). In the 360 mg group, compared with placebo, symptom severity (EEsAI) improved ($P < .05$), while the mean change in DSD composite score approached significance ($P = .055$). The most frequently reported adverse events in the overall study were headache, upper respiratory tract infection, arthralgia, nasopharyngitis, diarrhea, and nausea.

Conclusion: Compared with placebo, RPC4046 improved mean and peak eosinophil counts, histopathologic parameters, endoscopic features, and symptoms in steroid-refractory EoE patients, providing support that, in this subpopulation, RPC4046 markedly improves multiple measures used to evaluate EoE. In the overall study population, RPC4046 was generally safe and well tolerated.

OA0172 | Molecular restoration in eosinophilic esophagitis patients after treatment with proton-pump inhibitors

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Background: Eosinophilic esophagitis (EoE) is an emerging disease in children and its incidence is increasing over last years. EoE is a chronic inflammatory disorder characterized by esophageal dysfunction and eosinophilic inflammation. EoE has a persistence of ≥ 15 eosinophils per high-powerfield (eos/hpf). Proton-pump inhibitor (PPI) therapy, elimination diet and swallowed topic steroids are considered therapeutic options to treat this disorder. So, the aim of this study is to investigate the molecular changes in esophagus biopsies from pediatric children with EoE before and after the treatment with esomeprazole (a PPI-drug).

Method: The study was conducted with pediatric subjects from 3 to 15 years of age who fulfilled criteria for EoE diagnosis. Esomeprazole (2 mg/kg per day) was administered for 8 weeks. Healthy children were used as controls. Proximal esophagus biopsies were collected from patients before PPI-treatment and 8 weeks after treatment start, and they were used to RNA and protein isolation.

A set of 14 genes (*EGF*, *CCL26*, *IL5*, *IL13*, *POSTN*, *TSLP*, *TGFB1*, *VEGFA*, *SOCS3*, *CCR3*, *MAPK1*, *FLG*, *RNASE3* and *PRG2*) was evaluated by RT-qPCR. Moreover, protein levels of periostin, eotaxin-3 and filaggrin were measured by western blot. Gene and protein expression was compared between subjects diagnosed for EoE prior to esomeprazole administration and patients with EoE remission after PPI-treatment.

Results: Pediatric patients with EoE showed partial (> 5 and < 15 eos/hpf) or complete (< 5 eos/hpf) histological remission after treatment with PPI-drug. Gene expression was compared between EoE subjects before PPI-treatment and children treated with esomeprazole. We found a significant decrease of *CCL26*, *IL5*, *IL13*, *POSTN* and *PRG2* ($P < .05$-$.01$), and an increase with statistical significance of *FLG* ($P < .01$) in patients with EoE after PPI-treatment. Also, a significant rise ($P < .05$) was detected in protein levels of filaggrin in patients with PPI-administration compared to EoE subjects before PPI-treatment, supporting gene expression results.

Conclusion: The increase in *CCL26*, *IL5*, *IL13*, *POSTN* and *PRG2* gene expression, and the decrease in filaggrin gene expression and protein levels identified in children with EoE in relation to healthy controls were restored after PPI-treatment.

OA0173 | Markers of esophageal epithelial-mesenchymal transition are significantly reduced in active EoE following 16 weeks of treatment with RPC4046, an anti-interleukin-13 monoclonal antibody

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Background: The HEROES study evaluated RPC4046 in adults with active eosinophilic esophagitis (EoE). In this exploratory substudy, we investigated whether RPC4046 modulates epithelial-mesenchymal transition (EMT).

Method: Esophageal biopsy sections were taken at baseline and week 16 from 69 patients receiving weekly subcutaneous RPC4046 360 mg (n = 26), 180 mg (n = 19), or placebo (n = 24). Slides were stained by duplex immunofluorescence for e-cadherin and vimentin, counterstained nuclei with DAPI, and scanned at 20x via multispectral digital microscopy. A machine-learning algorithm mapped each slide's epithelial compartment. Nuclear, cytoplasmic, and membrane areas of each epithelial cell were defined and fluorescence intensity of each marker on a per-cell basis was recorded. Endpoints included change from baseline in percentage of vimentin-positive epithelial cells, change in total e-cadherin expression/cell, and change in vimentin:e-cadherin ratio/cell.

Results: Change from baseline in mean percentage of vimentin-positive cells was −4.24%, −2.75%, and −0.94% for RPC4046 360 mg, 180 mg, and placebo, respectively ($P < .05$, 360 mg vs placebo). Change in mean e-cadherin expression per cell was 101.6, 102.4, and 18.3, respectively ($P < .05$, each dose group vs placebo). Change in vimentin:e-cadherin ratio was significantly different from zero for 360 mg (−0.30) and 180 mg (−0.18) ($P < .05$). Similar effects for all markers were observed in each esophageal sampled region.

Conclusion: RPC4046 significantly improved esophageal tissue EMT markers in patients with EoE, with a greater effect observed with 360 mg. Results support the hypothesis that prevention of IL-13 binding to receptor subtypes IL-13Rα1 and IL-13Rα2 favorably impacts inflammatory and remodeling pathways and may reduce development of esophageal fibrostenosis in EoE.

OA0174 | Evaluation of the drug hypersensitivity reactions in the geriatric population

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Background: Comorbidities and multiple medication usage are common in the geriatric age group. The adverse drug reactions seen in this age group may cause problems leading to morbidity and even mortality. The aim of this study is to investigate the potential risk factors which could influence the likelihood and severity of anaphylaxis in drug hypersensitive geriatric patients.
Method: 119 patients aged older than 65 years who were admitted to our adult allergy clinic due to drug hypersensitivity reactions were included in the study. For the diagnosis skin prick and intradermal and patch tests as well as single blinded placebo-controlled drug provocation tests (SBPCDPT) with culprit drugs were performed. In non-steroidal anti-inflammatory drugs (NSAIDs) hypersensitive patients, SBPCDPTs with aspirin were performed to distinguish cross-reactive patients from selective ones. Patients were grouped as anaphylaxis and non-anaphylaxis and the anaphylaxis group was further divided as severe and non-severe according to literature. Demographic and clinical features including the reaction types, culprit drugs and comorbidities were compared between the groups.
Results: The mean age of the patients was 68.9 ± 4.1 and 78.2% of the patients were female. Comorbidities were observed in 74 (62.2%) patients. The most common comorbidities were hypertension (42.9%), and diabetes mellitus (13.4%). 16% of the patients were atopic. In 99 (83.2%) patients, immediate type hypersensitivity reactions were observed. The most common reaction types were urticaria (67.2%) and angioedema (26.9%). Anaphylaxis was observed in 34 (28.6 %) patients, and 19 of these were severe. The most common types of culprit drugs were NSAIDs (48.7%) and antibiotics (42%). In 12, 26, 2 and 16 patients, skin prick, intradermal, patch tests and SBPCDPTs were positive. There was no significant difference between anaphylaxis and non-anaphylaxis group regarding age, gender, comorbidities, the culprit drugs and skin test positivity with the culprit drugs. However, we observed that diabetic patients had more severe anaphylaxis than the non-diabetic patients (37.5%; 12.6% respectively; $P = .022$).
Conclusion: The most common drug reactions observed in our geriatric population were urticaria and angioedema. Our study showed that presence of diabetes may lead to severe anaphylaxis, which needs to be confirmed with more comprehensive studies.

OA0175 | Anaphylaxis to clavulanic acid: Frequency and clinical characterization

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Background: Drug-induced anaphylaxis (DIA) to beta-lactam antibiotics (BL) is one of the most frequent causes of DIA. The combination of amoxicillin (AX) and clavulanic acid (CLV) is widely used in clinical practice and although most allergic reactions are due to AX, selective reactions to CLV can occur. Aim: To evaluate the frequency and describe the clinical characterization of case reports and the drug allergy work-up activity in patients with anaphylaxis to CLV.
Method: Systematic review of patients with clinical history of DIA to BL referred to our drug allergy center from January 2011 to June 2018. These patients were studied according with ENDA/EAACI recommendations. Skin prick tests and intradermal tests (IDT) were performed for: PPL/MD, Penicillin G, AX and cefuroxime; other BL were tested according suspicion. In patients with suspected anaphylaxis to CLV, it was added purified CLV extract (DAP® Clavulanic, Diater). Drug provocation tests (DPT) were performed with the culprit drug, when previous investigation was negative, or with an alternative BL.
Results: 6 patients had confirmed anaphylaxis to CLV, corresponding to 3.6% of the total cases of DIA (n = 166) and 9.7% of DIA to BL (n = 62). All these patients (median 39 years (17-69), 4 females) had cutaneous symptoms associated with respiratory, gastrointestinal or cardiovascular symptoms. Diagnosis was confirmed in 5 patients by positive IDT to CLV and in one patient by positive DPT with CLV (negative IDT), resulting in an anaphylactic reaction (cumulative dose 25 mg), that resolved with IM adrenaline. Four patients had positive IDT to CLV, with negative tests for other BL and negative DPT with AX; one patient had both IDT tests positive to AX and CLV. Selective anaphylaxis to CLV was confirmed in 5 patients, with negative DPT to AX, corresponding to 15.6% of DIA after taking the association AX-CLV (n = 32). The patient with anaphylaxis to both compounds (CLV and AX) performed DPT with cefuroxime, which was negative.
Conclusion: Almost all confirmed cases of CLV anaphylaxis were IgE mediated. In these situations, skin tests with purified CLV extract have shown to be very useful. These patients should always be studied in specialized centers in order to guarantee a proper diagnosis and find suitable drug alternatives. To evaluate the selective hypersensitivity to CLV turns out to be extremely important, allowing the use of other BL like penicillin or AX in daily clinical practice.

OA0176 | Selective hypersensitivity reactions to NSAIDs and differences between pharmacological groups

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Background: Selective hypersensitivity reactions (SHR) are the second most frequent NSAID-induced hypersensitivity. Our aim was to analyzed symptoms, diagnostic methods and differences between culprit drugs in patients with NSAIDs SHR.

Method: Patients included were classified as single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA) or single-NSAID-induced delayed hypersensitivity reactions (SNIDR) whether the symptoms appeared less or more than 24 hours after NSAIDs administration. Diagnose was achieved if patients referred ≥ 2 episodes with one NSAID pharmacological group and tolerated acetylsalicylic acid (AAS) or indomethacin (if AAS implied) confirmed by drug provocation test (DPT); if < 2 episodes, DPT with culprit drug was also performed. In metamizole-induced- SNIUAA, skin tests (STs) were performed, and if negative a basophil activation test (BAT).

Results: We included 518 adult patients (66% female); 468 (90.3%) were SNIUAA and 50 (9.7%) were SNIDR. Patients suffered a median of 2 SHR episodes; the percentage of patients with only 1 episode was significantly higher in SNIDR (SNIDR 44% vs. SNIUAA 19.65%; $P < .0001$) and with ≥ 3, in SNIUAA group (SNIUAA 29.05% vs. SNIDR 10%; $P = .004$). Pyrazolones and arylpropionic acids (AP) were the most frequent culprit drugs for SNIUAA (39.7%, $P = .003$) and SNIDR (46.8%, $P > .05$) respectively. Anaphylaxis was the most frequent entity in SNIUAA and maculopapular exanthema (MPE) in SNIDR. Analysis by specific group drugs determined that pyrazolones induced most frequently anaphylaxis, MPE and fix drug exanthema (FDE); AP, immediate angioedema, MPE (mostly by dexketoprofen and ibuprofen) and FDE (mostly by naproxen and ketoprofen); arylacetic acids, anaphylaxis and immediate urticaria, in similar proportion; ASA and oxicams, immediate angioedema; paracetamol, immediate urticaria; and etofenamate, contact eczema. DPT confirmed diagnosis in 11.2% patients and history of repeated episodes in 60.4% (76.3% SNIDHR vs 63.6% SNIUAA, $P > .05$). STs with metamizole were positive for 72% SNIUAA and for 57.1% SNIDHR ($P > .05$). BAT was positive in 25.8% metamizole-induced SNIUAA patients.

Conclusion: Pyrazolones were the most frequently drugs involved and the principal cause of anaphylaxis. Development of better diagnostic tools and relevant clinical differences between NSAIDs groups may contribute to achieve diagnosis.

OA0177 | Are skin tests for general anesthetics necessary in atopics and patients with other drug allergies?

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Background: The necessity of preoperative skin tests with general anesthetic drugs in atopic patients and patients who have experienced other drug allergies is not known. The aim of the study was to determine the specificity and negative predictive value of skin tests of general anesthetic drugs in atopic patients, in patients who have drug allergies other than anesthetics and in those who have previously tolerated general anesthesia.

Method: A database programme on computer was formed to collect the preoperative allergy diagnostic data of the patients who have admitted to our outpatient allergy clinic between 2013-2018 were recorded in this database and to include all the possible perioperative drug reactions. Accordingly, detailed clinical history, diagnostic prick and intradermal test results, medications implemented in the perioperative period and the reactions were recorded.

Results: 402 out of 1167 patients fulfilled the inclusion criteria of having proper information for further evaluation. 75.9% (305/402) of the patients were female and the mean age was 45.9 ± 14.5 years. History of hypersensitivity reactions (HRs) due to NSAIDs and/or antibiotics, radiocontrast agents, local anesthetics, cosmetics and food were 46.5% (n = 187) , 4.2% (n = 17), 1.5% (n = 6), 0.2% (n = 1) 2.2% (n = 9) respectively. 75, 63 and 52 patients had chronic urticarial, allergic rhinitis and asthma, respectively. The negative predictive values of skin tests for general anesthetics in atopic patients and in those who have tolerated anesthesia were shown in Table 1 and the specificity of the skin tests for each general anesthetic was shown in Table 2. Only 3 patients with preoperative negative skin tests experienced HRs during operation.

Conclusion: The high rates of negative predictive value and specificity of skin tests with general anesthetic drugs in atopic patients, in those with allergy to other drugs and in patients who have previously tolerated general anesthesia reveal the controversial indication of skin tests in these patient groups.

TABLE 1 the negative predictive values of skin tests for general anesthetics in atopic patients

Patients with drug hypersensitivity(n = 187)		Total of patients DST(n)	DST positive patients(n)	DST negative patients (n)	Using the drug (n)	True negative count(n)	NPV(%)
Patients with drug hypersensitivity(n = 187)							
Barbiturates	Thiopental sodium	41	0	41	3	2	
Opioids	Morphine	22	0	22	17	17	
	Fentanyl	182	0	182	171	171	100
	Remifentanil	80	1	79	40	40	100
Benzodiazepines	Midazolam	173	0	173	170	170	100
Phencyclidine	Ketamine	9	0	9	2	2	
Other	Propofol	182	4	178	150	150	100
NMB	Atracurium	45	0	45	4	3	
	Mivacurium	38	0	38	8	8	
	Vecuronium	7	1	6	1	1	
	Rocuronium	181	1	180	137	137	100
	Cisatracurium	2	0	2	0	-	
Succinylcholine	Suxamethonium	8	0	8	1	1	
Narcotic analgesic	Tramadol	136	0	136	47	47	100
Atopic patients (n = 215)							
Barbiturates	Thiopental sodium	45	1	44	8	–	
Opioids	Morphine	26	0	26	23	–	
	Fentanyl	205	1	204	195	195	100
	Remifentanil	111	1	110	59	59	100
Benzodiazepines	Midazolam	205	2	203	191	191	100
Phencyclidine	Ketamine	13	0	13	11	11	
Other	Propofol	206	6	200	168	167	91.2
NMB	Atracurium	50	1	49	3	2	
	Mivacurium	32	0	32	2	2	
	Vecuronium	23	0	23	2	2	
	Rocuronium	207	1	206	177	177	100
	Cisatracurium	5	0	5	1	1	
Succinylcholine	Suxamethonium	10	1	9	0	–	
Narcotic analgesic	Tramadol	162	0	162	42	42	100

TABLE 2 The specificity of the skin tests for each general anesthetic

Previously received general anesthetic (n = 229)		Total of patients DST (n)	DST positive patients (n)	DST negative patients (n)	Using the drug (n)	True negative count (n)	Specificity (%)
Barbiturates	Thiopental sodium	47	0	47	4	3	
Opioids	Morphine	21	0	21	21	21	
	Fentanyl	222	1	221	208	208	99.5
	Remifentayl	107	1	106	54	53	98.1
Benzodiazepines	Midazolam	215	1	214	206	205	99.5
Phencyclidine	Ketamine	9	0	9	9	9	
Other	Propofol	222	6	216	178	178	96.7
NMB	Atracurium	60	0	60	4	3	
	Mivacurium	37	0	37	3	3	
	Vecuronium	11	1	10	1	1	
	Rocuronium	221	2	219	179	179	98.8
	Cisatracurium	0	0	0	0	0	
Succinylcholine	Suxamethonium	8	0	8	1	1	

Previously received general anesthetic (n = 229)		Total of patients DST (n)	DST positive patients (n)	DST negative patients (n)	Using the drug (n)	True negative count (n)	Specificity (%)
Narcotic analgesic	Tramadol	165	0	165	54	54	100

OA0178 | Perioperative anaphylaxis in children: Etiology, time sequence and patterns of reactivity

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Background: This is the first study to examine time sequence of physiologic variables and clinical signs of perioperative anaphylaxis (PA) in children. The goals were to describe characteristics of PA, identify any clinical patterns of allergic reactivity, and ascertain differences between causative drugs. Better understanding how PA presents may facilitate earlier recognition and treatment, thus reducing morbidity.

Method: We performed a retrospective audit of anaesthesia records from paediatric patients with PA from six centres in the United Kingdom, France and the United States over a period of ten years. Time sequence of vitals and signs of PA were obtained from anaesthetic charts. Reaction severity was determined using the lowest recorded systolic blood pressure (sBP) and total amount of adrenaline administered. The results of allergy testing evaluations were also reviewed.

Results: A total of 29 children with PA were included. Mean age was 11 years, with 16 (55%) girls and 13 (45%) boys. Based on the modified Ring and Messmer Grading Scale, severe reactions were seen in 25 (86%) children, with 4 (14%) experiencing cardiac arrest requiring cardiopulmonary resuscitation. All grade 4 and 80% of grade 3 cases had onset of clinical signs of PA within 10 minutes of exposure to the causative agent. Hypotension was the first clinical feature of PA in 59% of cases, followed by tachycardia and bronchospasm. In 16 (55%) cases, the presenting signs of PA involved multiple organ systems. The lowest recorded sBP was 30 mmHg. Thirteen (45%) children had oxygen saturations less than 85%. The median number of doses of adrenaline, not counting infusions, was 3.7 (range, 1-14); median doses for grade 3 and 4 reactions were 100 mcg (range 0.3-3656) and 2573 mcg (range 50-5746), respectively. Mean time from initial PA treatment to adrenaline administration was 6.6 min (SD 3.7, range 5-15). Neuromuscular blocking agents (NMBA) were the most common cause of PA. Patients with NMBA-induced PA tended to receive higher cumulative amounts of adrenaline (P = .056) than patients with antibiotic-induced PA.

Conclusion: Life-threatening hypotension is frequently the first presenting sign of PA in children. There are no clinical predictors with regard to the severity of imminent PA. The most commonly identified causative drugs were NMBA. Further studies should aim to optimise the prediction, identification and early management of PA in children.

OA0179 | Hypersensitivity reactions to anesthetics in children

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Background: Hypersensitivity reactions to anesthetic drugs are not so often but they can be very severe and life threatening. Identifying the cause of hypersensitivity reactions during anesthesia remains challenging because of the multitude of medications involved.

Method: The purpose of our study was to confirm or rule out the diagnosis of hypersensitivity to anesthetic drugs in children.

Results: Of 120 children referred to the Drug Allergy Unit of University Children's Hospital of Belgrade, in the last 15 years, 60 (50%) were boys and 60 (50%) were girls. The ages ranged from 1.5 years to 17 years (mean age 8.42). 39 (32.5%) children were testing to local anesthetics, 71 (59.17%) to general anesthetics and 10 (8.33%) children were testing to both. We performed allergy work up according EACCI recommendation to all drugs that were given to patient during anesthesia. Out of the total of 49 tested children to local anesthetics: 9 (18.37%) were positive and 40 (81.63%) were negative. Clinical reactions to local anesthetics were urticaria: 6 (66.66%), urticaria with bronchospasm: 2 (22.22%) and angioedema: 1 (11.11%).

Out of total 81 (67.5%) tested children to general anesthetics, 56 (69.14%) were positive and 25 (30.86%) were negative. Various clinical reactions were described as being induced by general anesthetics (the number of patients affected is shown in parentheses): urticaria (49), urticaria and angioedema (13), urticaria and bronchospasm (9), angioedema (6), anaphylaxis (4). Positive allergy work ups were at 28 out of 40 tested to midazolam (70%), 26 out of 46 tested to atropine (56.52%), 9 out of 11 tested to ketamine (81.82%), 5 out of 20 tested to sodium thiopental (25%), 4 out of 32 tested to fentanyl (12.5%). We also perform allergy work up to muscle relaxants and 19 out of 44 test were positive (43.18%).

Conclusion: In all children with suspected hypersensitivity reactions to anesthetic drugs, it is necessary to perform complete allergy work-up to all drugs that were given to patient during anesthesia.

TUESDAY, 4 JUNE 2019
OAS 31
BIOMARKERS IN PRECISION MEDICINE IN ASTHMA

OA0180 | Serum MiRNA expression is associated with asthma control and airway inflammation in non-elderly asthmatics

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Background: MicroRNAs are small noncoding RNA molecules, involved in regulation of various biological processes, including inflammation. miRNA expression has been associated with asthma treats, but a role for serum miRNA as a biomarker of disease activity and control has not been fully evaluated. We aimed to assess association of miRNAs, selected by profiling, with asthma control and airway inflammation in elderly and non-elderly asthmatics.

Method: In fifty-nine asthmatic patients (AP)- 31 aged 30-50 years and 28 above 65 years old- asthma control and pulmonary function were assessed and FeNO was measured. Expression miRNAs in serum was measured with Real-time PCR and concentrations of cytokines (IL-6, IL-8, IL-10, TNFα and TNF RI) were assayed with ELISA.

Results: Elderly AP, as compared to non-elderly asthmatics, had higher serum expression of miRNA -126a (−0.28 ± 1.3 vs. −1.31 ± 0.86; $P < 0.001$) and miRNA-106a (0.47 ± 1.19 vs. −0.01 ± 0.45, $P = .01$). Serum miRNA −126a and miRNA-106a expression correlated with age (r = .38, $P < .0$ and r = .29, $P < .05$; respectively). In non-elderly, but not in the elderly AP, expression of selected miRNAs was associated with the level of asthma control and airway inflammation. Patients with uncontrolled disease (according to GINA or ACT) had lower serum miRNA-126a and miRNA-106a, while patients with history of asthma exacerbation in the past 12 months had significantly lower expression of miRNA-106a. ACT correlated with miRNA-126a (r = .44, $P < .05$) and with miRNA-106a (r = .45, $P < .05$). FeNO concentration in non-elderly AP was negatively correlated with miRNA-146a (r = −.41, $P < .05$), −126a (r = −.6, $P < .05$) and −106a (r = −.62, $P < .05$).

Serum TNF RI concentrations in all asthmatics correlated with miRNA-106a (.44, $P < .05$) and miRNA -126a (r = .41, $P < .05$), while in non-elderly patients there was positive correlation between serum level of TNF RI and miRNA −146a (r = .38, $P < .05$), −126a (r = .37, $P < .05$) and −106a (r = .38, $P < .05$).

Conclusion: Serum miRNA expression is age related and in younger asthmatics is associated with asthma control and bronchial inflammation. Serum miRNAs should be considered as potential biomarkers of asthma control.

OA0181 | Novel metabolomic biomarkers associated with HDM-allergic asthma severity

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Background: HDM is a major perennial allergen source and a significant cause of allergic rhinitis and allergic asthma. Prevalence data for HDM allergen sensitization vary from 65 to 130 million persons in the general population worldwide to as many as 50% among asthmatic patients. Available treatments with glucocorticoids, Immunotherapy and biological drugs are used in groups with mild o or moderate asthma. However, these treatments are not enough to control exacerbations in severe asthmatic patients. Moreover, the identification of HDM-asthmatic patient's phenotypes and follow-up of treatment effects require novel biomarkers elucidation.

Method: Three groups of patients were included: Group 1, non-allergic patients exposed to HDM. Group 2, HDM-allergic patients with mild asthma treated and controlled with CT . Group 3, HDM-allergic patients with severe asthma treated but not controlled with CT, IT Xolair. Plasma was collected from the patients and its metabolic profile was obtained using Liquid Chromatography coupled Mass Spectrometry (LC-MS) in both positive and negative modes.

Results: LC-MS detected 1378 and 658 chemical signals in positive and negative modes. From those, 833 and 565 complied with the quality criteria. Principal component analyses (PCA) of the two different polarities separated clearly the uncontrolled patients (group 3) from both the controls (group 1) and HDM controlled patients (Group 2). However, PCA did not find any difference between group 1 and 2.

Conclusion: Our results show a model that clearly stratified HDM-allergic patients according to the severity of the disease, by identifying a group of metabolites useful as biomarkers with predictive value.

OA0182 | Relationship between lung function abnormalities, blood and bronchoalveolar lavage biomarkers and airway structural changes in asthma

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Background: Airway structural changes (remodeling) are important in asthma pathology and may result in fixed airway obstruction and its symptoms. The aim of the present study was to identify potential biomarkers of airway remodeling for means of patient selection for novel therapies targeting the process.

Method: The study included 105 white adult asthmatics (53 with fixed obstruction). We determined cross-sectional geometry of two distal and two peripheral bronchi, quantified low-attenuation lung area (LAA%) and established patient clusters. Bronchoalveolar lavage (BAL) and endobronchial biopsy with mucosa histological examination as well as patient sera were obtained. Blood and BAL biomarkers including IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-17A, IL-23, INF-gamma and periostin, as well as circulating ADAM33, were measured and interplay between them, airway anatomy, histology and lung function studies was investigated.

Results: Patients with fixed airflow limitation were characterized by lower lumen area, higher airway area, increased wall area ratio (WAR) and wall thickness ratio of peripheral bronchi, accompanied by raised LAA%. They also had increased neutrophil and eosinophil counts in blood, increased BAL eosinophilia, higher blood levels of fibrinogen, INF-gamma, periostin, and ADAM33. Blood neutrophilia, increased serum HDL-cholesterol, TSH, urea, and extended activated partial thromboplastin time were laboratory determinants of thicker reticular basement membrane (RBM) of bronchial mucosa. BAL eosinophilia was the only positive predictor of collagen I accumulation. Surprisingly, we observed a negative correlation between RBM thickness and collagen I deposit. Cluster analysis based on cross-sectional geometry of peripheral bronchi revealed three well-separated clusters, characterized by different lung function parameters, biomarker levels, collagen I deposit and RBM thickness.

Conclusion: Unfavorable airway structural changes were related to the type 2 immunity, higher ADAM33, INF-gamma and neutrophil count in peripheral blood. Thicker RBM might play a protective role against collagen I accumulation and bronchial mucosa fibrosis.

OA0183 | Human volatilome analysis using ENose to assess uncontrolled asthma in a clinical setting

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Background: Exhaled breath volatile organic compounds (EB-VOC) analysis has shown promising results when discriminating individuals with asthma. Currently, there are no biomarkers of uncontrolled asthma. Therefore, we aimed to assess, in a real clinical setting, the ability of EB-VOC, analyzed by an electronic nose (eNose) to identify individuals with uncontrolled asthma.

Method: A cross-sectional study was conducted and breath samples from 199 participants recruited during regular appointments in an outpatient clinic (130 females, aged 6 to 78, 66% with asthma) were analysed using eNose (Cyranose 320®). A multivariate unsupervised cluster analysis, using resistance data from 32 sensors, was able to discriminate three VOC patterns clusters. The observations from the validation set were then assigned individually to each cluster according to the training model. Between-cluster comparisons were performed using ANOVA, Kruskal-Wallis and chi-squared tests.

Results: In the training set (n = 121) three different clusters regarding asthma, lung function, symptoms in previous four weeks and age were identified. Pairwise comparisons between clusters showed significant differences for chest tightness during exercise, dyspnoea, and gender. These findings were confirmed in the validation set (n = 78), where the training model algorithm identified three clusters with similar characteristics. Participants with less reported respiratory symptoms, less night awakenings and dyspnoea, were grouped in one cluster while, in the others, participants showed similar poor control of symptoms. Additionally, we observed a significant difference in the distribution of subjects with asthma despite the presence of asthmatics in all clusters.

Conclusion: The analysis of the EB-VOC profile by eNose may be used as a fast and non-invasive complementary screening tool for uncontrolled asthma in clinical settings.

OA0184 | Role of osteopontin in late-onset asthma

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Background: Late-onset asthma (LOA) is associated with poor clinical outcome and rapid lung function decline. Osteopontin (OPN) is a multifunctional cytokine expressed in various cells and increases with age and respiratory infections. We hypothesized that OPN may be involved in the phenotype of LOA and investigated its role in subjects with LOA compared to early-onset asthma (EOA).

Method: We enrolled 131 adult asthmatics (48 LOA, 83 EOA) and 226 healthy controls (HC) from Ajou Medical Center (Suwon, South Korea) and collected sera samples. As an *in vitro* setting, human airway epithelial cells (HAECs) were stimulated by Poly(I:C). As an in *vivo* setting, we set up 2 models of ovalbumin (OVA)-induced asthma, younger asthma at 6 wks (OVA-6 wk) and older asthma at

12 wks (OVA-12 wk) compared to two controls, 6 weeks (C-6 wk) and 12 weeks (C-12 wk). Levels of OPN, interleukin (IL)-8, transforming growth factor (TGF)-β1, and YKL-40 (chitinase 3-like I) in sera of study subjects, cell-free supernatants and bronchoalveolar lavage fluid (BALF) of mice were measured by ELISA. Gene expression of *Spp1* in the lungs of mice was evaluated by SYBR®Green.

Results: Serum level of OPN was significantly higher in asthmatics than HC ($P < .001$) and in asthmatics with LOA than those with EOA ($P = .002$). Moreover, positive correlations were noted between OPN and age (r = .441, $P < .001$), IL-8 (r = .282, $P < .001$), TGF-β1 (r = .174, $P = .012$) and YKL-40 (r = .264, $P = .008$). ROC analysis showed that serum OPN level is a significant serum marker for differentiating LOA from HC with 91.4% sensitivity and 52.7% specificity ($P < .001$). Poly(I:C) induced release of OPN, IL-8, TGF-β1 and YKL-40 from HAECs ($P < .05$ for all), which were attenuated by the treatment of dexamethasone and montelukast. Although airway hyperresponsiveness (AHR) of C-12 wk was similar to that of C-6 wks, OVA-12 wk showed increased AHR and total cells/eosinophil counts in the BALF compared to those of OVA-6 wk. The OPN level in the BALF and expression of *Spp1* of OVA-12 wk was higher than those of OVA-6 wk or NC-12 wk ($P < .05$ for all)

Conclusion: Respiratory viral infections and aging may induce OPN release from HAECs, contributing to developing the phenotype of LOA.

OA0185 | YKL-40 As biomarker in severe asthma

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Background: Complex or multifactorial diseases such as asthma are associated with genetic predisposition, lifestyle and environmental factors. YKL-40 is a chitinase-like glycoprotein encoded by the *chitinase 3-like 1* gene- *CHI3L1- with a Cytogenetic location: 1q32.1*. Serum YKL-40 have been reported to be a biomarker for severe asthma and reduced lung function. However, serum YKL-40 could also be associated with age, sex, tobacco smoke exposure and obesity. The aim of this study is to evaluate the degree to which serum and/or sputum YKL-40 are correlated with these factors and hence their suitability as a biomarker of airway disease in a cohort of severe asthmatic patients.

Method: In 243 severe asthmatic (BTS 4 and 5) adult subjects (48.9 ± 14.2 years) from the Wessex Severe Asthma Cohort (WSAC) (170 female; 74 male), spirometry was performed according to BTS/SIGN guidelines and sputum induction with inhaled hypertonic saline was undertaken in 111 subjects. Serum and sputum YKL-40 were determined in duplicate using the microvue YKL-40 EIA kit-ELISA (Quidel corporation, San Diego, California, USA). Statistical analysis was undertaken with SPSS (v22); statistical significance was defined as $P < .05$.

Results: Serum YKL-40 has a weak correlation with age (Spearman's rho 0.395; $P = .000$); with gender (male: 137 ng/mL ± 100 ng/mL; female: 114.4 ng/mL ± 102.4 ng/mL; $P = .000$); smoking pack years (Spearman's rho 0.250; $P = .000$); and current status smoking (never smoker: 106.73 ng/mL ± 76.35 ng/mL; ex-smoker: 130.97 ng/mL ± 102.27 ng/mL; current smoker: 204.91 ng/mL ± 208.9 ng/mL; $P = .002$). Sputum YKL-40 levels were not related with age or adverse lifestyle. Serum or sputum YKL-40 were not associated with oral corticosteroids therapy and not correlated with BMI.

Conclusion: Sputum YKL-40 levels in severe asthmatics are likely to be a better biomarker, than serum YKL-40, of airway inflammation and asthma severity.

TUESDAY, 4 JUNE 2019
OAS 32
CHARACTERIZATION AND MECHANISMS OF FOOD ALLERGENS

OA0186 | Identification of gibberellin-regulated protein as a new allergen in cherry allergy

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Background: Cherry allergy has recently been reported to be cross-reactive to other fruits of the *Rosaceae* family and tree pollens. To date, four cherry proteins have been registered as cherry allergens by the WHO/International Union of Immunology Societies: Pru av 1 (pathogenesis-related protein, PR-10), Pru av 2 (thaumatin-like protein), Pru av 3 (nonspecific lipid transfer protein), and Pru av 4 (profilin). However, it is still unclear whether gibberellin-regulated protein (GRP) (which has been identified as a new allergen in other fruit allergies, such as peaches and oranges) also involve cherry allergy. We investigated the allergenicity of cherry GRP in cherry allergy and clarified the clinical characteristics of cherry GRP allergy.

Method: Twenty-five patients (M:F = 3:22, mean age 34.9 yrs) diagnosed with cherry allergy based on relevant clinical history, positive skin prick test (SPT) and/or challenge test were enrolled. We purified cherry GRP using ion-exchange chromatography. To evaluate the allergenicity of the purified cherry GRP, we performed enzyme-linked immunosorbent assay (ELISA), basophil activation tests (BATs) and SPTs with purified cherry GRP. ELISA was also performed with purified peach GRP, nPru p 7. Using ImmunoCAP (Thermo Fisher Scientific), we measured specific IgE levels against cherry, rPru p 1, rPru p 3, and rPru p 4.

Results: The ELISA using cherry GRP showed positive reactions in 11 of 25 patients (44.0%), whereas using nPru p 7 showed positive reactions in 6 of 18 patients. Seventeen patients provided additional informed consent for BATs and SPTs using cherry GRP. BATs and SPTs showed positivity for cherry GRP in 4 and 6 patients, respectively. The positivity for specific IgE against cherry, rPru p 1, rPru p 3 and rPru p 4 was 76.0% (19/25), 68.0% (17/25), 0% (0/25), and 20.0% (5/25), respectively.

The most frequent symptoms of cherry GRP allergy were facial swelling and oropharyngeal symptoms. One patient experienced anaphylactic shock after the ingestion of cherry, followed by running. In 6 patients with positive SPT results with cherry GRP, 6, 2, 2 or 6 patients had a history of pollinosis, bronchial asthma, atopic dermatitis or allergy to a plant-derived food, especially the *Rosaceae* fruits such as peaches, respectively.

Conclusion: Cherry GRP may be involved in cherry allergy and may be cross-reactive to GRPs from the *Rosaceae* family fruits.

OA0187 | IgE to epitopes of Ara H 2 enhance the diagnostic accuracy of Ara H 2-Specific IgE

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Background: The utility of allergen-specific IgE (sIgE) assays to diagnose peanut allergy has improved with sIgE to individual peanut allergens, such as Ara h 2; however, there are still cases that cannot be accurately diagnosed with such tests. Using a semi-quantitative peptide microarray, we have recently identified 7 peptides from Ara h 1, 2 and 3 that are bound more by IgE of peanut allergic (PA) than by IgE of peanut sensitised but tolerant (PS) individuals. We aimed to quantify sIgE and specific IgG4 (sIgG4) to the 7 peptides using ImmunoCAP technology and to assess their diagnostic performance.

Method: PA, PS and non-sensitized non-allergic (NA) patients were studied (n = 105). Unblocked peptides (JPT Peptide Technologies) were conjugated to the solid phase of ImmunoCAP by Thermo Fisher. sIgE and sIgG4 binding was quantified using the Phadia 100. Diagnostic model comparisons were performed using likelihood ratio tests between each specified nominal logistic regression models using SAS version 9.4 and JMP Pro 14.

Results: sIgE to 4 of the 7 identified peptides on Ara h 1 (n = 2), 2 (n = 4) and 3 (n = 1) was significantly higher in PA than in PS patients (*P* values of .1001, .2804, <.001, .5427, <.001, .001 and .004 respectively). The differences in IgE binding were independent of peanut-sIgE levels. A combination of sIgE to the 4 peptides of Ara h 2 showed strong diagnostic discrimination between allergic and non-allergic subjects with an area under ROC curve (AUC) of 0.839 and improved (*P* = .0002) the diagnostic accuracy of Ara h 2-sIgE (AUC = 0.906) when combined with the Ara h 2 sIgE (AUC = 0.934). sIgE to peptides from Ara h 1 or Ara h 3 did not offer significant advantage compared to the sIgE to the respective allergen. Ratios of IgG4/IgE to 5 out of the 7 peptides were higher in PS than in PA subjects, with *P* values of .0564 and .1651 for Ara h 1 peptides, <.001, .9627, <.001, <.001 for Ara h 2 peptides and < .001 for the Ara h 3 peptide.

Conclusion: Peptides from Ara h 1-3 were bound preferentially by IgE of PA than by IgE of PS patients, who had higher IgG4/IgE ratios. Ara h 2 peptide-specific IgE enhanced the diagnostic accuracy of Ara h

2-specific IgE. Ability of peptide-specific IgG4 to surmount their IgE counterpart seems to be important in established peanut tolerance.

OA0188 | Allergenicity and cross-reactivity of different variants of the peanut allergen Ara H 2

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Background: Ara h 2 is considered to be the major peanut allergen, showing high clinical relevance in peanut allergic patients. Studies have shown that denaturation of Ara h 2 reduces its allergenicity, suggesting that the potency of Ara h 2 is dependent on its globular structure. If a reduction in allergenicity can be combined with a retained immunogenicity, modified versions of Ara h 2 may be an interesting target for allergen-specific immunotherapy. Thus, the aim was to produce different Ara h 2 variants and evaluate their immunogenicity, allergenicity and cross-reactivity, using a Brown Norway (BN) rat model.

Method: Recombinant versions of Ara h 2 (r.Ara h 2) were produced using the BL21 (DE3) *E. coli* strain, and subsequently chemically (c.r.Ara h 2) or enzymatically (e.r.Ara h 2) refolded. In addition, denatured Ara h 2 (d.Ara h 2) was obtained from native Ara h 2 (n.Ara h 2) by reduction and alkylation. CD spectroscopy, SDS and native PAGE were performed for structural analyses. BN rats were i.p. immunised three times with n.Ara h 2, d.Ara h 2, c.r.Ara h 2 or e.r.Ara h 2. Immunogenicity, allergenicity, avidity and cross-reactivity were evaluated by means of different ELISAs and the clinical reactivity was analysed by an ear swelling test.

Results: Different degrees of folding were shown for the four versions of Ara h 2, n.Ara h 2 being fully folded and d.Ara h 2 without any globular structure. Both versions of recombinant Ara h 2 were shown to contain mixtures of Ara h 2 with various degree of folding. All Ara h 2 variants could induce specific IgG1 antibodies, though to different degrees, with unfolding resulting in an almost 400-fold reduction in immunogenicity. All variants of Ara h 2 except for d.Ara h 2 had a strong sensitising capacity, confirming previous findings that allergenicity of Ara h 2 is dependent on its globular structure. No cross-reactivity was found between n.Ara h 2 and d.Ara h 2, whereas c.r.Ara h 2 and e.r.Ara h 2 showed cross-reactivity with each other as well as with n.Ara h 2 and d.Ara h 2, indicating intermediate folding. Clinical reactivity was detected in n.Ara h 2 and e.r.Ara h 2 immunised animals when tested with n.Ara h 2, whereas no significant clinical reactivity was observed when testing with d.Ara h 2.

Conclusion: Allergenicity as well as immunogenicity of Ara h 2 is dependent on its globular folding, indicating that modified Ara h 2 version with reduced allergenicity is associated with a concomitant reduction in tolerogenicity.

OA0189 | Late reaction in Gal-Alpha-Gal allergy is reflected in serum levels after ingestion of pork kidney

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Background: Allergy to Gal alpha gal (GAG) is a rare type-1 allergy, where sensitization apparently is linked to tick-bites and where symptoms mainly occur hours after ingestion of mammalian innards or meat, e.g. pork, beef and lamb. The mechanism behind the late reaction-pattern is unclear, i.e. whether the delaying is due to slow absorption, encapsulation in lipoproteins, slow release or exerted Tat effector-cell level. Our aim was with an indirect method to investigate serum levels of GAG allergens after ingestion of pork-kidney being a main source of GAG with peanut as reference allergen.

Method: Six healthy volunteers ingested with minimum 1-week separation 100 gr. defatted peanut-flour suspended in water, 87 gr. blended, raw pork-kidney as a smoothie or 87 gr. fried pork-kidney with vegetable garniture. Blood samples were drawn at baseline (t = 0) and repetitively at 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 24 h after ingestion. Donor basophils were stripped-off IgE and passively sensitized using sera containing high IgE titer against peanut or GAG, respectively. Basophils were incubated with the serum samples in 12 dilutions and residual cellular histamine was measured by the glass fiber method and results expressed as per cent Histamine Release (HR). Differences in release were tested with Wilcoxon signed rank sum to HR-values normalized to equal max-release (100%).

Results: Max releases were for peanut reached after 2 hours, 3 hours for pork-kidney-smoothie and 6 hours for pork-kidney. Time to 50 % of max release, T½max, was extrapolated to 22 min, 50 min and 2 hours for peanut, smoothie and pork-kidney respectively. There was a significant difference in HR and thereby in absorption between peanut and smoothie after 30 min and 1 h, between peanut and pork-kidney after 15 min, 30 min, 1 h and 2 h, and smoothie and pork-kidney after 1 h and 2 hours.

Conclusion: This study shows that HR from basophils can be used to detect serum-levels of allergenic proteins. The measured levels of absorbed allergen from peanut and fried pork-kidney reflect the clinical situation in peanut and GAG allergy; peanut is measurable in serum 15 min. after ingestion, whereas pork-kidney levels are only detected much later. By changing the matrix of pork-kidney into a blended, drinkable smoothie, absorption speed increased indicating that the late reaction of GAG might be influenced by passage-timing of the stomach.

OA0190 | IgE-reactive proteins defined by 88 fish-allergic children, predicting the allergenicity of 66 Asia-Pacific fish species

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Background: Fish allergy is often a life-long disease with high frequencies of anaphylaxis. Diagnostics and management are hampered by a large number of under-investigated fish species. The aim of this study was to quantify four recognised allergens in 66 Asia-Pacific fish species as well as to identify all IgE-reactive proteins in 12 most consumed species defined by 88 Australian children with clinically confirmed fish allergy.

Method: Raw and heated protein extracts from muscle tissue of 66 fish species were prepared and analysed for their allergen content by SDS-PAGE and immunoblotting using allergen-specific antibodies. All 88 patients were skin-tested to seven fish species and serum IgE reactivity to 12 fish species was compared. Antibody-reactive bands were excised and analysed by advanced mass spectrometric analyses.

Results: The fish allergens; parvalbumin, tropomyosin, collagen and aldolase A, were detected in over 90% of the 66 species studied by immunoblotting. All 12 of the most commonly consumed fish species contained at least four IgE-reactive proteins. IgE-reactive proteins were identified by mass spectrometric analyses and the amino acid sequence was retrieved from the recently published genome of the respective species, allowing their registration with the WHO/IUIS (www.allergen.org). The most IgE-reactive protein was parvalbumin, followed by tropomyosin. Other prominent IgE-reactive proteins include collagen, aldolase, enolase, glyceraldehyde-3-phosphate dehydrogenase, creatine kinase, myosin light chain, L-lactate dehydrogenase, and triosephosphate isomerase. Fish species frequently consumed in the Asia-Pacific including Asian seabass, basa catfish, salmon and tilapia demonstrated higher IgE reactivity compared to Atlantic cod. Cartilaginous fish samples contained fewer allergens, corresponding to weaker IgE reactivity.

Conclusion: This is the largest cohort of fish-allergic individuals undergoing molecular characterisation to a comprehensive panel of fish allergens. Our results contribute to a better understanding of the abundance and cross-reactivity of specific allergens in a variety of fish species, leading to better diagnostics and management of this life-threatening disease. A fast, reliable and efficient approach for identifying IgE-reactive proteins is presented, which can be applied to many fields in the area of food allergy. Further research is needed to extend the list of registered fish allergens and clarify their clinical relevance.

OA0191 | Egg yolk acts as adjuvant activating innate immune responses to egg white allergens in BALB/C MICE

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Background: The development of food allergy is a multifactorial process that is not only influenced by the allergen. Some dietary compounds, such as lipids, could act as adjuvants in food allergy sensitization. In eggs, egg white (EW) proteins are considered to exhibit the highest allergenic potential. However, the main components of egg yolk (EY) are lipids, which stand among the extrinsic factors that modify the allergenic properties of proteins. The aim of this study was to investigate the adjuvant effect of EY in the development of sensitization to EW proteins.

Method: BALB/c mice were orally exposed to PBS, cholera toxin (10 µg), EW (50 mg), EY (100 mg), and their mixture EW:EY (50:100 mg) during four days. After euthanasia by CO_2 inhalation, samples from duodenum, jejunum, Peyer's patches (PP), and mesenteric lymph nodes (MLN) were collected to analyse mRNA expression of *Il33*, *Il25*, *Tslp*, *Il4*, *Il13*, *Gata3*, *Irf4*, and *Irf8* by RT-qPCR. Bone-marrow-derived dendritic cells (BM-DCs) were exposed to EW, EY, and EW:EY and cocultured with T cells. Proliferating Th1 and Th2 cells were analysed by flow cytometry.

Results: Mice orally exposed to the mixture of EW and EY upregulated duodenum and jejunum expression of *Il33*, *Il25*, *Tslp* and *Il4*, compared with mice administered EW and EY separately, in a way similar to that exerted by cholera toxin. Administration of either EY or the EW:EY mixture promoted the intestinal expression of *CD1d1*, a molecule involved in the innate pathway of presentation of lipid antigens to invariant NKT cells triggering Th2 responses. Furthermore, EW:EY significantly increased the expression of *Il13*, *Gata3* and *Irf4* in the PPs, as compared with EW and EY alone. Similarly, a Th2-bias was also observed in the MLNs. Stimulation with EW:EY primed BM-DCs to promote the proliferation of Th2 cells.

Conclusion: EY exerts Th2-biasing effects through the modulation of innate immune signals that may enhance the susceptibility to develop sensitization to EW proteins.

OA0192 | Surfactant protein A (SP-A) reduces human rhinovirus C (RV-C)-induced inflammation responses and viral replication in pediatric nasal epithelial cells

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Background: RV-C is associated with increased hospitalization rates of children from lower respiratory tract diseases and is also linked to exacerbation of chronic lung diseases. SP-A is a protein of the bronchoalveolar compartment that binds to numerous pathogens and regulates innate immunity. We hypothesized that SP-A interacts with RV-C15 and affects the virus elicited inflammatory cytokine production and viral replication in differentiated nasal epithelial cells derived from asthmatics and non-asthmatics children.

Method: SP-A was purified from bronchoalveolar lavage fluid obtained from adult alveolar proteinosis patients, by affinity chromatography, using mannose sepharose. SP-A binding to solid phase RV-C15 was measured by anti-SP-A ELISA. Nasal epithelial cells obtained by intranasal brushings, from children between the ages of 10-16 were propagated, and subsequently differentiated for 21 days using an Air-Liquid Interphase (ALI) method. Differentiated cells were exposed to RV-C15 in the present or absent of SP-A (50 - 400 ug/ml). Cytokine secretion was determined by ELISA, and viral replication and expression of IFNλ, CXCL11, IRF-7 and MDA-5 were measured by qRT-PCR.

Results: SP-A binds RV-C15 with an apparent Kd of 0.48 nM. RV-C15 infected, replicated, and released infectious particles into the apical phase of the ALI cultures. In the presence of SP-A, the transcription of IFNλ, IRF-7 and MDA-5 were significantly reduced. SP-A also reduced CXCL11 expression and secretion. In addition, SP-A inhibited viral replication in differentiated nasal epithelial cells from asthmatics and non-asthmatics pediatric individuals.

Conclusion: These data illustrate the novel anti-viral and anti-inflammatory properties of SP-A, which may also be useful for reducing Rhinovirus-induced exacerbation of asthma and COPD.

OA0193 | Antiviral immune response deficiency of nasal epithelial cells from asthmatic patients after RV1B infection

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Background: This study aimed a.to establish a robust cell culture model for studying rhinovirus (RV) infection and the consequent epithelial responses in asthma and rhinitis and b.to study the molecular mechanisms in primary nasal epithelial cells (PNECs) from asthmatics that drive in increase propagation of RV.

Method: First, a comparison of fresh and cryopreserved PNECs (n = 3) before and after RV infection was conducted (RNAseq analysis). Then, synchronized paired and matched nasal and bronchial ECs from healthy (n = 3) and asthmatic (n = 6) individuals compared throughout the course of RV1B infection events, measuring virus replication, interferon pathway (RT-QPCR and Luminex)) and cytotoxicity levels. After the model establishment, cryopreserved PNECs from 6 asthmatics and 6 healthy subjects were infected with RV1B (0 h, 3 h and 6 h) and RNAseq was performed. The interferon pathway was further studied at 6 h, 8 h, 24 h and 48 h post RV1B infection. Provided written informed consent for all patients.

Results: The antiviral pathways are intact in cryopreserved cells and induced as much as in fresh. Specific gene expression strongly correlates between fresh and cryopreserved cells of the same individual. There were no significant differences between PNECs and PBECs in the mRNA expression levels of any interferon-related gene and the virus replication and cytotoxicity levels didn't differ significantly in paired AECs. Healthy and asthmatic uninfected PNECs showed 140 differential expressed genes (DEGs). The higher expression of Wnt pathway implicated genes in asthmatic PNECs are correlated to subepithelial fibrosis and airway remodelling. After RV1B infection the antiviral pathways TNF, NFkappaB signaling pathways are activated quicker in healthy PNECs (3 h) than asthmatics (6 h), and in lower levels. Also, the reduced expression of IRF7 and increased expression of SOCS1 in asthmatics, resulting in inhibition of activation of main antiviral pathways. The IFN deficiency in asthmatic PNECs is verified and followed by increased viral replication and cytotoxicity.

Conclusion: Our data indicate that cryopreserved PNECs are a suitable cell culture model for studying RV infection responses. The RV infections are more frequent in asthmatics due to differential gene regulation of essential pathways. There is an inadequate onset of antiviral pathways that would limit the infection early, decreased interferon production and extensive persistent inflammation with increased cell death in the asthma epithelium.

OA0194 | RNA sequencing revealed transcriptomic changes of the human nasal epithelium following human influenza infection

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Background: With the advent of RNA sequencing technology, we are able to study host transcriptomic changes in more detail. We previously established using microarray an *in vitro* differentiated human nasal epithelial cells which serves as a model to study primary host- viral interaction at the nasal epithelium. The objective of the study is to further build on the model to query for transcriptomic changes using RNA sequencing of the influenza infected human nasal epithelium.

Method: Building on the microarray results, here we performed increased number of samples with RNA sequencing where 10 samples of human nasal epithelial cells from different healthy donors were used to establish the common nasal signatures post human influenza infection. We performed differential gene analysis followed by pathway gene set enrichment analysis to elucidate the key changes occurring in the nasal epithelium following infection.

Results: With RNA sequencing, we profile an increased number of significantly differentially expressed genes from the nasal epithelium and identified and verified additional transcripts tied to the immune responses against human influenza infection. The immune pathways were largely tied to viral response, interferon pathway, MAPK pathway and NFκB pathway. We also performed focused analysis on non-immune response transcripts to identify key non-immune pathways found unique to the nasal epithelium, the primary site of influenza infection. Pathways found to be differentially regulated include apoptotic, responses to fatty acid and organic cyclic compound metabolism.

Conclusion: In conclusion, RNA sequencing analysis of human influenza infected nasal epithelium revealed early response pathways of the nasal epithelium against influenza virus infection and may be used as a healthy baseline comparator for target discovery as well as comparing with influenza infection with underlying chronic inflammatory airway conditions.

OA0195 | MV130, a polybacterial mucosal preparation, protects mice against experimental viral infections inducing trained immunity

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Background: Recurrent wheezing affects one third of children, being a global health problem with considerable expenditure and impact on quality of life. Virtually all wheezing attacks (WA) in young children are of viral etiology. Their prevention is a major concern as effective therapies are still lacking. MV130 has been shown to reduce recurrent WA in a randomized, double-blind, placebo-controlled clinical trial (EudraCT number: 2012-002450-24). However, the mechanism underlying the clinical benefit conferred by MV130 in viral infections remained unknown. The aim of this study was to assess the effect of MV130 in experimental viral respiratory infections and to gain insight into the possible immune mechanism(s). Specifically, a role for trained immunity was addressed.

Method: Mice were immunized intranasally (i.n.) with MV130 or excipient, and, subsequently, challenged (i.n.) with Vaccinia or flu virus. Body weight, survival and lung viral load were evaluated. Trained immunity was analyzed *in vivo* and *in vitro* using different hallmarks of trained immunity including protection to *Candida albicans* in immunodeficient mice, cytokine production and epigenetic reprogramming.

Results: MV130 increased the resistance to viral intranasal infection, enhancing survival and decreasing lung viral titers. Protection was also found against lethal *Candida albicans* infection in mice lacking functional T and B cells, demonstrating that it was mediated by innate immune cells. In addition, *in vitro* experiments carried out on human monocytes indicated that training with MV130 in the presence of MTA, an epigenetic inhibitor, abolishes TNF-α production, a hallmark of trained immunity.

Conclusion: MV130 induces trained immunity and protects against viral experimental infections because of this fact. Thus, MV130 may be acting as a trained immunity-based vaccine (TIbV)[1] enhancing the functional response of innate immune cells.

1.-Sanchez-Ramon et al. (2018). Trained immunity-based vaccines: a new paradigm for the development of broad-spectrum anti-infectious formulations. Front. Immunol. 9:2936. https://doi.org/10.3389/fimmu.2018.02936

OA0196 | Microbiome correlates of success of treatment of atopic dermatitis with the JAK/SYK inhibitor ASN002

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Background: Staphylococcus aureus (S aureus) dominated skin microbiome dysbiosis plays an important role in Atopic dermatitis (AD). Recently, a novel oral JAK/SYK inhibitor, ASN002, demonstrated significant decreases in EASI scores over 4 weeks of treatment. However, the impact of JAK/SYK inhibition on AD-associated microbiome is still not clear. Here, skin microbiome was analyzed in a clinical trial of ASN002 in AD patients to investigate the microbiome correlates of success of treatment.

Method: Moderate-to-severe AD patients received ASN002 for 28 days in a double-blind randomized phase-1b study with doses: 20, 40 and 80 mg daily and placebo (N = 9 per arm). Skin microbiome from lesional (LS) and non-lesional (NL) skin swabs at days 1, 29 and 43 were sequenced by NGS (16S V1-3).

Results: At baseline in LS skin S aureus was the dominant species (frequency 0.21-0.98) in 60% of patients. S. aureus frequency in LS skin was higher ($P < 0.001$) than in NL skin. Higher *S.aureus* baseline frequency in LS was the major cause for microbiome dysbiosis and was significantly ($P < 0.001$) associated with higher EASI score at baseline.

A significant ($P = 0.005$) dose-dependent decline in *S.aureus* frequency in LS was exhibited at day 29 in 86% of patients, in comparison to placebo (33%), and correlated with EASI decline (R = 0.7, $P = 0.003$). Moreover, lower *S.aureus* frequency at baseline, and at end-of-treatment, significantly ($P < 0.001$) predicts sustained low EASI at day 43.

Conclusion: JAK/SYK inhibition with ASN002 gives rise to reduction in *S.aureus* frequency in AD patients, although direct blocking effect on *S.aureus* is not expected. Conversely, lower baseline *S.aureus* frequency predicts ASN002 success of treatment. This supports the hypothesis that *S.aureus* takes advantage of disrupted barrier to over-colonize the skin; by reducing Th2/Th22 inflammation ASN002 allows barrier healing and consequently reduces S.aureus. Further combined microbiome-transcriptome analysis in our study will be used to verify this hypothesis.

OA0197 | Modulation of the myeloid arachidonic acid metabolism imparts helminth-driven control of type 2 inflammation

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Background: Type 2 immune responses drive host defense against helminth parasites, but also cause allergic inflammation. Lipid mediators derived from arachidonic acid (AA) are key effector molecules of type 2 inflammation. Here, we sought to determine whether helminth parasites can directly modulate AA metabolic pathways and thereby regulate type 2 inflammation.

Method: Mice were infected with an intestinal helminth (*Heligmosomoides polygyrus bakeri*, *Hpb)* or treated with *Hpb* extract ("*HpbE*") during house dust mite (HDM)-induced allergic airway inflammation. Human monocyte-derived macrophages (MDM) and granulocytes (PMN) or mouse bone marrow-derived macrophages (BMDM) were treated with *HpbE*. Mediator profiles were determined by LC-MS/MS (eicosanoids) or multiplex assays (cytokines) and type 2 inflammation was assessed *in vivo* (histology, cytospins) or *ex vivo* (human chemotaxis assays).

Results: We show that *Hpb* infection results in the anti-inflammatory modulation of the AA metabolism by inducing a shift from 5-lipoxygenase to cyclooxygenase (COX) metabolism. In macrophages, *HpbE* suppressed the production of leukotrienes, but induced the p38 MAPK-, NFkB- and HIF-1α- dependent production of anti-inflammatory mediators (IL-10 and PGE_2), which resulted in the suppressed recruitment of human granulocytes. Treatment with *HpbE* or transfer of *HpbE*-conditioned macrophages attenuated allergic airway inflammation in mice in a COX-2-dependent fashion.

Conclusion: Our findings show that helminths can regulate type 2 inflammation by modulating the eicosanoid output of innate immune cells. Anti-inflammatory modulation of the AA metabolism by helminth products may be translated into new immunomodulatory strategies for the treatment of type 2 inflammatory diseases.

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OA0198 | Omalizumab in spontaneous food tolerance in adult patients

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Background: Food allergy affects up to 8% of population (7), of these, up to 20-30% can be refractory to treatment. (9) With Omalizumab´s widespread use, its effect on food allergy has drawn allergist´s attention. It has been used in multiple studies in food allergy in children as an adjunct therapy for OIT (3,4,5,6). These studies have shown promising results in achieving tolerance, by allowing faster, safer and higher doses of oral immunotherapy (OIT) (7). However, question remains on how long should omalizumab be carried on. Also, little has been said on the utility of omalizumab as single treatment in food allergy in adult population. Pena et al presented a study where omalizumab was used as monotherapy for 10 allergic children (milk and egg) who received omalizumab during 16 weeks and 4 tolerated single-blind food challenges. (1) We present our findings regarding food allergy evolution in six adult patients receiving omalizumab either for the treatment of asthma or chronic urticaria (CU) as well as an off-the-label treatment for food allergy.

Method: In the course of 8 years, we have treated up to 73 patients with omalizumab (asthma, urticaria or off-label). We have complete data on 6 patients receiving this treatment with the diagnosis of food allergy either as the main indication or as an associated diagnosis (3 with off-label indication for food allergy; 1 chronic urticaria, 2 asthma).

Results: Five patients were female; with an average age of 38.3 y-o. The most common food allergens were nuts, fruits, vegetables, legumes, fish and shellfish. Total IgE ranged from 85 UI/mL to 1,113 UI/mL (average 414.5 UI/mL). Most patients had recurrent anaphylaxis as a manifestation of food allergy which caused a great impact on their quality of life. Patients received omalizumab adjusted to total IgE levels (asthmatic) or standard dose recommended for CU with increasing interdose periods. Patients have been receiving omalizumab for as far as 2009. Open food challenges (OFC) were started on week 16 of omalizumab. Only two patients have had mild symptoms during OFC with apple and strawberry, all other OFC were well tolerated. In the present, all 6 patients are able to follow a restriction-free diet.

Conclusion: Although omalizumab has not been stopped, and question remains on when to do so, in our experience omalizumab alone has facilitated tolerance to certain foods in patients with food allergy.

TABLE 1 Demographic data

Subject	Gender	Age (y-o)	Total IGE (UI/mL)	Initial dose	Current dose	Diagnosis
1	F	58	107	300 mg /28 days	300 mg/ 28 days	FA
2	M	35	382	300 mg /14 days	300 mg/ 42 days	FA
3	F	43	300	300 mg /28 days	300 mg/ 28 days	FA
4	F	25	1,113	600 mg /14 days	300 mg/ 56 days	ASTHMA
5	F	25	85	150 mg /14 days	150 mg/ 28 days	ASTHMA
6	F	44	500	300 mg /14 days	300 mg/ 42 days	CU
7	F	29	216	300 mg /28 days	300 mg/ 56 days	FA
8	F	47	148	300 mg /28 days	300 mg/ 56 days	FA
9	M	41	210	300 mg /28 days	Suspended Jul. 2018	FA
10	F	18	350	150 mg/28 days	150 mg/28 days	ASTHMA
11	M	44	738	300 mg /28 days	300 mg /70 days	CU
12	F	27	242	300 mg/28 days	300 mg /56 days	CU
13	M	13	587	600 mg/28 days	Suspended Feb. 2018	ASTHMA
14	F	30	325	300 mg/28 days	300 mg/28 days	FA

Abbreviations: CU: chronic urticaria; FA, food allergy.

OA0199 | The immunological signatures of success or failure following peanut oral immunotherapy combined with individualized omalizumab treatment in peanut allergic adolescents

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Background: Peanut allergy is a major cause of anaphylaxis, hence effective treatment strategies are warranted. Our previous work has shown that individualized omalizumab treatment (OT), allows a safe initiation and rapid up-dosing of pOIT in severe peanut allergic adolescents. After treatment, 11 out of 17 patients safely passed an open peanut challenge (treatment successes). Preliminary results indicate that baseline peanut-specific IgE antibodies, as well as, the amplification of peanut-specific IgG4 antibodies during treatment might predict treatment outcome. In order to increase our understanding of the immunological signatures leading to treatment success, we aimed to longitudinally follow the B cell immune responses underlying the combined OT and pOIT treatment. Subsequently, these responses were compared between treatment failures and successes.

Method: PBMCs were collected at several timepoints during treatment; before starting OT (baseline), at the peanut challenge during OT and prior to starting pOIT (challenge), at maintenance dose pOIT prior to OT reduction (stepdown), and at the final peanut challenge without OT for 12 weeks (final visit). B cells frequencies and phenotype were studied by flow cytometry. Moreover, IgE, IgG4 and IgG secreting B cells were determined by enzyme-linked immunospot.

Results: B cells frequencies and phenotypes (naïve, memory, and FoxP3 expressing B cells) did not change over treatment time and did not differ between treatment failures and successes either. Nevertheless, treatment failures showed significantly higher frequencies of plasma blasts at the challenge timepoint, as well as, trends towards higher levels of IgE secreting B cells at all timepoints, whereas the levels of IgG4 secreting B cells did not differ.

Conclusion: These results suggest that the combined OT and pOIT did not affect the general B cell phenotype. Moreover, our results show that the general B cell compartment is not decisive for treatment success. Nevertheless, our results might indicate a higher IgE secreting B cells activity in the treatment failures, which will be investigated more in future experiments. Moreover, future research will focus on T cell responses underlying the treatment outcomes. Understanding these immunological signatures underlying treatment failure and success will guide us further towards a personalized and effective treatment for severely peanut allergic patients.

OA0200 | Targeting birch allergy with monoclonal IgG antibodies that bind allergen and prevent IgE effector cell activation

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Background: Birch allergy is estimated to affect over 100 million people worldwide. Bet v 1 is the immunodominant and most abundant allergenic protein in birch pollen. Blocking a specific allergen with monoclonal antibodies was recently shown to be effective in preventing an allergic response using a cocktail of 2 antibodies to Fel d 1, the primary cat allergen (Orengo, 2018). Using a similar approach, herein we demonstrate that a cocktail of three Bet v 1 specific antibodies is sufficient to prevent initiation of the birch allergic response.

Method: Bet v 1 specific IgG4 monoclonal antibodies REGN5713, REGN5714 and REGN5715 were isolated from Regeneron's VelocImmune human antibody mouse platform and evaluated singly and in combination for their ability to bind Bet v 1 and prevent effector cell activation. Inhibition of basophil activation was evaluated using a flow cytometry based phosphoflow assay and blockade of mast cell degranulation was assessed using the passive cutaneous anaphylaxis (PCA) mouse model in wild type or mice genetically modified to replace endogenous *FceR1a* with the corresponding human sequence.

Results: REGN5713, REGN5714 and REGN5715bind Bet v 1 simultaneously and with high affinity. The three-antibody cocktail, REGN5713-5714-5715, achieved maximal blocking efficacy in all formats evaluated. REGN5713-5714-5715 inhibited ³90% of basophil activation in 9/10 birch allergic donors, while REGN5713-5715, the best dual antibody cocktail, achieved the same magnitude of inhibition in 4/10 donors. In the PCA model when using mouse serum as the source of polyclonal Bet v 1 specific IgE, the combination of REGN5713-5714-5715 achieved 100% blockade of mast cell degranulation. Notably, REGN5713-5714-5715 blocked mast cell degranulation induced by the related tree pollen allergen from hornbeam as well as extract from 3 different birch species. In a humanized PCA model using human plasma containing polyclonal birch specific-IgE, REGN5713-5714-5715 blocked mast cell degranulation to a greater extent than REGN5713-5715 achieving ³90% blockade in 4/5 as compared to 1/5 donors evaluated.

Conclusion: These data confirm the immunodominance of Bet v 1 in the allergic response to birch pollen and suggest that maximal blockade of Bet v 1-induced allergy may be achieved with REGN5713-5714-5715. Applying this approach to other allergens may enable development of a repertoire of anti-allergen therapeutics for personalized allergy management.

OA0201 | Inhibition of mast cells with a Siglec-8 antibody reduces tissue damage in models of skin and lung fibrosis and COPD

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Background: IL-33 stimulation of mast cells is believed to play a role in tissue remodeling in lung, skin, and gastrointestinal fibrosis and chronic obstructive pulmonary disease (COPD). Siglec-8 is an inhibitory receptor selectively expressed on mast cells and eosinophils. Siglec-8 monoclonal antibodies (mAb) have been previously shown to inhibit IgE-mediated mast cell activity in vivo; however, the activity of a Siglec-8 mAb has not been evaluated in models of fibrosis or COPD.
Method: The activity of a Siglec-8 antibody was evaluated in a chronic, 30-day, subcutaneous, bleomycin-induced fibrosis model and a 12-week cigarette smoke (CS) induced COPD model in Siglec-8-transgenic mice. A Siglec-8 mAb was therapeutically dosed 14 days post bleomycin treatment or starting at week 8 in the experimental COPD model. Human lung and skin tissue from non-diseased subjects or lung tissue from COPD subjects were dissociated into single cells and used for ex-vivo assays.
Results: Therapeutic treatment with a Siglec-8 mAb significantly inhibited progression of bleomycin-induced fibrosis as evidenced by reduced lung weights, infiltration of leukocytes into bronchoalveolar (BAL) fluid and decreased expression of TGFβ1 and IL-13 in skin lesions. Therapeutic treatment with a Siglec-8 mAb also substantially suppressed CS-induced experimental COPD. Siglec-8 mAb treated groups displayed reduced neutrophil infiltration in BAL fluid and significantly improved lung function. In addition, Siglec-8 mAb attenuated activation of mast cells in ex-vivo human lung and skin tissue induced by IL-33 and TSLP.
Conclusion: Siglec-8 mAb treatment decreased tissue damage in multiple animal models and inhibited mast cell activation by IL-33 and TSLP. An anti-Siglec-8 approach may have the potential to treat fibrotic diseases, COPD, or diseases caused by elevated IL-33 or TSLP.

OA0202 | Molecular, structural and mechanistic insight into ligelizumab mediated suppression of IgE dependent allergic responses

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Background: Allergen-specific IgE plays a major role in the development of allergic reactions. It binds with high-affinity to the primary IgE receptor FcεRI on allergic effector cells. Upon exposure to the cognate allergen, IgE-loaded allergic effector cells immediately degranulate and release soluble mediators causing allergic symptoms. On the other hand, IgE interacts with FcεRII/CD23 on antigen presenting cells and B-cells and thereby regulates antibody production. The therapeutic anti-IgE antibody omalizumab, which is approved to treat moderate-to-severe asthma and chronic spontaneous urticaria, is known to neutralize free IgE and to prevent binding of IgE to FcεRI as well as FcεRII. A new high affinity anti-IgE antibody, ligelizumab, is being developed with the intention to overcome some of the limitations associated with omalizumab. Here, we assessed the binding characteristics of ligelizumab on a molecular and cellular level and explored functional consequences.
Method: Using crystallography we determined the exact binding epitope of ligelizumab on IgE. The binding kinetics to IgE were verified by surface plasmon resonance and the efficacy of ligelizumab to block the interaction of IgE with either FcεRI or FcεRII on primary human basophils and B-cells, respectively, was determined by flow cytometry. Basophil activation tests and ELISpot assays were performed to functionally compare ligelizumab to omalizumab.
Results: The structure of the IgE:ligelizumab complex revealed binding across the IgE dimer, with each variable region forming interactions with both Cε3 domains on IgE. The higher affinity of ligelizumab for IgE as compared to omalizumab was due to lower off-rates. Whereas ligelizumab was more efficient in blocking the IgE:FcεRI, this was not the case for the IgE:FcεRII interaction. Moreover, ligelizumab was superior to omalizumab in preventing allergen-induced basophil activation as well as inhibiting IgE production by B cells.
Conclusion: Ligelizumab and omalizumab recognize different, however, closely related binding regions on IgE. As a consequence, they greatly differ in their functional activity. Our data suggest that ligelizumab will be significantly superior to omalizumab in suppressing IgE-mediated allergic reactions - but not CD23 mediated inflammatory activities - and thus might show substantially increased treatment efficacy in IgE/FcεRI-dependent allergy-related disorders.

OA0203 | Real-life study of patients treated with omalizumab for chronic spontaneous urticaria in France: 6-month data of the LUCIOL study

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Background: Chronic Spontaneous Urticaria (CSU) is defined by onset of itching papules and/or angioedema with longer than

6 weeks evolution and no known cause. LUCIOL study is a post-listing study, requested by the French Health Authorities, in order to assess the use of Omalizumab (OMA) in the treatment of CSU on real-life conditions. Interim results at 6 months are presented here.

Method: This is a national, multicenter, observational, prospective study of patients over 12 years of age for whom it was decided to initiate at inclusion visit OMA treatment for CSU. The primary efficacy was the proportion of patients with well-controlled CSU (disease activity score UAS7 ≤ 6) at 6 months (M6). The principal evaluation criteria were the quality of life evolution score (DLQI) and real-life conditions of use.

Results: The Full Analysis Set population consisted of 263 patients (mean age, 43.7 years, women, 66.2%, CSU with anti-H1 resistance, 91.6%). After 6 months of treatment, 68.8% of patients had a UAS7 ≤ 6 score (n = 202). The DLQI score decreased compared to baseline from −8.5 at M6. More than half of the patients (55.0%) had received previous CSU treatments other than only AH1: anti-leukotrienes (36.9%) and oral corticosteroids (18.3%). The delay between updosed AH1 and OMA initiation was greater than 4 weeks for 93.1% of patients. The initial prescription of OMA at dose labelled (300 mg every 4 weeks) was modified for 14.8% of patients (mainly for inadequate response) then at M6 for 38.4% of patients (mainly for improvement or remission). The frequency of injections was modified at M6 (increase of the time interval between injections for 82.5% of patients). Concomitant CSU treatments were continued after OMA initiation by 60.8% of patients. OMA administration was made at hospital at baseline for 77.4% of patients and then made by visiting nurse for 63.2% of patients at the 6th injection.

Conclusion: At 6 months, the real-life results of OMA on disease activity and improvement in quality of life were consistent with those observed in clinical studies. In real conditions of use, these data provided a preview on the treatment optimization and pointed out the need for improvement of recent European recommendation acceptance in France. The interim results of the LUCIOL study confirm the efficacy of OMA treatment in the CSU under real treatment conditions. The results at 1 year will provide more additional data on the real-life use of OMA in France.