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ORAL PRESENTATIONS

01 The ‘GA²LEN Sinusitis Cohort’: an introduction
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Background: The Global Allergy and Asthma European Network (GA²LEN) is a network of the leading European allergy clinical and research facilities and the GA²LEN Sinusitis Cohort is a database within this network. The aim of this cohort is to intensify research on rhinosinusitis pheno- and endotypes, thus differentiating chronic rhinosinusitis (CRS) into smaller disease entities based on clinical, biological, and patient-reported outcomes.

Methods: Patients (N = 869) from 9 participating outpatient ENT clinics recruited to participate in this cross-sectional, multicentre cohort study were assigned to 3 groups: CRS with nasal polyps (CRSsNP), both diagnosed using EPOS 2012 guidelines; and control defined as an unmatched cohort of patients undergoing nasal polyp surgery (CRSwNP) and CRS without nasal polyps (CRSsNP), both diagnosed using EPOS 2012 guidelines; and control defined as an unmatched cohort of patients undergoing nasal polyp surgery. Across groups, mean age was 42.1 years (range 15–76 years), 55.0% were male, and 95.5% were Caucasian. Comorbid allergic rhinitis was diagnosed in 33.2%, 29.0%, and 23.8% of patients in the CRSsWP, CRSsNP, and control groups, respectively. Of all patients, 33.2% had comorbid asthma, which was significantly (p < 0.0001) more frequent in the CRSsNP (49.6%) than CRSsNP (20.2%) group. CRSsNP patients reported late age of onset for asthma, whereas CRSsNP patients reported early age of onset. Among CRSsNP and CRSsNP patients who did not report asthma, 59.8% and 41.9%, respectively, had an FEV1/FVC ratio of ≤ 80% (p = 0.063). Contact allergy was present significantly more often in CRSsNP than CRSsNP patients (15.1% vs 5.2%; p = 0.0001). Overall, 4.4% of all patients reported aspirin intolerance, which was significantly more frequent in CRSsNP vs CRSsNP patients (7.4% vs 1.3%; p < 0.0001); among these CRSsNP patients, 90.9% had asthma, forming the Aspirin Exacerbated Respiratory Disease (AERD) subgroup. A significantly higher number of CRSsNP patients reported previous surgery vs CRSsNP patients (45.9% vs 22.7%; p < 0.0001).

Discussion: The GA²LEN Sinusitis cohort was not intended to be population representative; however, it is a large cohort of patients recruited throughout Europe with clinical, biomarker, as well as patient-reported outcomes.

02 A role for neuropeptides in innate immune inflammation of the nose
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Background: The airway epithelium constitutes the first line of defense in the protection against invading pathogens. It acts as a barrier, but it is also a major source of early released inflammatory mediators, which shape the inflammatory response. Neuropeptides, such as substance P (SP), have long been considered to be early contributors to the inflammatory response, causing pain hypersensitivity and vasoconstriction, as well as activation and infiltration of various immune cells. Toll-like receptor 7 (TLR7) is found on the epithelial cells and is known to be activated by viruses. The present study has investigated the relationship between TLR7 activation/expression and SP release/stimulation.

Method: Human nasal epithelial cells (HNEC) were obtained through nasal brushing of 6 healthy donors. The cells were cultured until passage 4 and thereafter stimulated with the TLR7 agonists R-837 or R-848 for 15min, 30 min or 4h. The subsequent release of SP was analyzed with Elisa. In addition, HNECs were stimulated with SP (10, 50 or 100nM) for 30 minutes in the presence or absence of NK-1 antagonist Aprepitant. Expression of Toll-like receptors was then determined using flow cytometry.

Results: HNECs produced substance P in a concentration-dependent manner in response to both R-837 and R-848. Increased levels of SP were detected already after 15 minutes, and increased successively over time. SP stimulation increased not only the TLR7 expression in HNECs, but also...
expression of TLR1, 4 and 9 on these cells. Apoptotic effectively blocked
this response.

Conclusion: The presented results suggest a role for SP in modulating
the local innate immune response in the nose.

O2
Thymic Stromal Lymphopoietin (TSLP) promotes human eosinophil-
basophilic in situ hemopoiesis, and its secretion from human nasal
epithelium is a function of TSLP genotype
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Background: Allergic diseases are characterized by tissue eosinophilic and
basophilic inflammation. There is substantial evidence that this particular
inflammatory profile results from the migration to tissues of a common
eosinophil-basophilic (Eo/B) progenitor that undergoes a differentiative
process regulated by local cytokines, termed in situ hemopoiesis. We
therefore investigated the role and mechanisms of TSLP involvement in
human Eo/B in situ hemopoiesis in relation to atopy. Also, since candidate
gene and genome-wide association studies have identified protective
associations between the single nucleotide polymorphism (SNP) rs1837253 in
the TSLP gene and risk for allergy, asthma and airway hyper-
responsiveness, we evaluated the secretion of TSLP protein from primary
nasal epithelial cells (NEC) in relation to rs1837253 genotype.

Methods: Peripheral blood CD34+ cells derived from atopic and nonatopic
individuals were stimulated with or without IL-3, IL-5, or GM-CSF and assessed
for Eo/B colony forming units (CFU) in both methylcellulose and nasal
epithelial/CD34+ cell air-liquid interface (ALI) co-cultures, and cytokine
surface receptor expression by flow cytometry. Genotyping was performed
using a commercially available TaqMan® genotyping assay.

Results: • TSLP preferentially enhanced IL-3/TNFα-dependent Eo/B CFU
from CD34+ cells;
• Eo/B CFU and TSLPR expression were significantly increased in atopic-
derived CD34+ cells post TSLP; (p<0.05) and IL-3-TSLP-stimulation
(p<0.001), compared to non-atopic-derived CD34+ cells;
• In progenitor/NEC ALI co-cultures, secreted TSLP was biologically active,
and sufficient to induce the differentiation of CD34+ cells into Eo/B CFU;
• There was decreased TSLP secretion by nasal epithelial cells obtained
from heterozygous (CT; 1.8-fold) and homozygous rs1837253 TSLP minor
allele (TT; 2.5-fold) individuals, compared to homozygous ‘wild-type’
individuals (CC; p<0.05).

Conclusions: These studies further support the concept of in situ
hemopoiesis and point out a previously unrecognized, critical role for TSLP
in the development of allergic upper airway inflammation and its role in
Eo/B differentiation, a link between adaptive and innate immunity. Novel
functional genomics of TSLP show that the rs1837253 polymorphism may be
directly involved in the regulation of TSLP secretion, providing explanations
for both genetic association studies and recently reported positive clinical
taxiing trials targeting TSLP in allergic asthma.

O4
Clinical changes induced by allergen immunotherapy with
dermatophagoides pteronyssinus in local allergic rhinitis
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Background: Allergen immunotherapy (AIT) is the etiologic treatment of
the allergic respiratory disease and has the ability to modify their natural
course. In this study we investigated the efficacy and safety of subcutaneous
AIT with Dermatophagoides pteronyssinus (DP) in local allergic rhinitis (LAR).

Methods: Thirty-six subjects with LAR to DP were selected to participate in
a double-blind, placebo-controlled, parallel-group, phase II clinical trial of
subcutaneous AIT in LAR. The patients were randomized to receive AIT-DP
with Pangermin PLUS, ALX, DP, or placebo for a period of 24 months. The
primary endpoint was total symptoms (TSS) and total medication scores
(TMS). Secondary endpoints were: total combined symptom+medication
scores (TCS), daily symptoms score (DSS), daily medication score (DMS),
médication free days (MFD), skin testing, nasal allergen provocation test
(NAPT-DP), and adverse events. Serum and nasal lavage samples were
obtained for immunological studies.

Results: AIT-DP induced a clinically relevant and significant improvement
compared to placebo with a 47% reduction in TSS (0.60 vs. 1.14; p<0.001)
and a 51% decrease in TMS (0.65 vs 1.34; p=0.002). At 6-12-18-24 months significant
improvements in TCS (p=0.046; p=0.037; p=0.011; p=0.007) and DSS
(p=0.003; p=0.012; p<0.001; p<0.001); and at 24 months in DMS (p=0.014),
and MFD (p=0.031) compared to placebo were also observed. AIT-DP
induced an increase in nasal tolerance to NPAT-DP at 6-12-18-24 months
(p=0.003; p<0.001; p<0.001; p<0.001) compared to placebo, with negative
NAPT-DP in the 50% of patients. One patient with AIT-DP had a local
moderate reaction solved without systemic treatment, no systemic reactions
occurred.

Conclusion: Subcutaneous allergen immunotherapy with Dermato-
phagoides Pteronyssinus has demonstrated to be an effective and well-
tolerated treatment in LAR. This phase II study provides the indication for AIT
in LAR. To our knowledge this is the first study carried out in patients with
LAR in patients sensitised to house dust mite.

O5
Expression profiling of nasal polyp epithelial cells identifies
two distinct phenotypes and suggests a role for neurogenic inflammation
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Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a chronic
inflammation of the nasal mucosa of unknown etiology. As airway epithelial
cells have a well-accepted role in the regulation of innate defence and other
local inflammatory processes we wanted to explore whether nasal polyp
epithelial cells could play a role in the pathophysiology of CrSwNP.

Method: Primary epithelial cells were isolated from nasal polyps of 24
affected individuals and from the middle turbinates of 9 healthy controls.
After a limited culture period RNA was extracted and the expression profile
determined using Human Genome U133 Plus 2.0 Genechip Array (Affymetrix
inc., Santa Clara, CA, USA). Supernatants collected from the epithelial cells
and immunohistochemistry on biopsies were used for validation.

Results: The expression pattern in nasal polyp epithelial cells showed an
aberrant expression for 23 genes compared to healthy controls. Furthermore,
the expression pattern suggests two distinct epithelial profiles
within the nasal polyp group. Detailed analysis of these two distinct profiles
reveals a deregulation of epithelial differentiation markers (KRTADP
and CNFN) and of key regulators of neurogenic inflammation (SLURP1,
LYNX1, and SLC4A4).

Conclusion: Our data identified neurogenic inflammation as a potential
novel player in the pathophysiology of CrSwNP and a possible dichotomy
of nasal polyp epithelial cells. The implications of these differences with
healthy epithelial cells are not yet fully understood, but merit further
investigation.

O6
Endoscopic sinus surgery improve quality of life and decrease
allergywism in patients with chronic rhinosinusitis -
a multi-centre study
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We have previously reported that chronic rhinosinusitis (CRS) has a significant impact on health-related quality of life (HRQOL). In this study we aimed to analyse whether sino-nasal symptom scoring can be used to predict the postoperative outcome measured by HRQOL. Secondly, we wanted to investigate whether absenteeism caused by sinus symptoms decrease after endoscopic sinus surgery (ESS). We also wanted to assess whether the duration of sinus disease had an effect on the outcome of ESS.

Methods: Two hundred and seven patients with CRS with and without nasal polyps (NP) admitted for ESS from ten hospitals were enrolled. EPOS2012 definitions of CRS and NP were used. The patients completed the short-form 36-item questionnaire (SF-36), the 22 Sinonasal Outcome Test (SNOT-22) and a total Visual Analogue Scale (VAS) regarding rhinosinusitis symptoms preoperatively, 6 and 12 months after surgery.

Results: Of the 207 patients, 135 were diagnosed with CRS+NP and 72 CRS-NP. Sixty-nine percent of the population had anterior ethmoidectomy, 36% posterior ethmoidectomy and 24% of the frontal sinus recess. The quality of life scores measured by SF-36 improved in all eight domains but one after surgery. The total SNOT-22 score decreased significantly from 51.8 ± 33.0 to 6 months postop (p<0.0001) and stayed at this level 12 months after surgery. There was no statistically significant difference in total SNOT-22 scoring between patients with and without NP, but in four of the SNOT-22 questions there were differences. The total VAS scores diminished from 67 ± 33 postoperatively. Sick-leave due to rhinosinusitis dropped from 8-14 days to 1-7 days months after ESS. The questions on “Lack of a good night’s sleep” and “Frustrated/restless/irritable” in SNOT-22 were predictive (p=0.001) for the postoperative total SNOT-22 score, when performing a backwards stepwise regression analysis. Those patients who had had a history of less than 12 months of sinus disease scored best postoperatively measured by SNOT-22.

Conclusion: Quality of life improved significantly after ESS measured by SF-36, SNOT-22 and VAS. Scoring of two of the questions in SNOT-22 proved to be significantly predictive for the postoperative outcome. Patients with CRS±NP reported less absenteeism due to sino-nasal disease 12 months postoperatively. The patients with shorter sinus disease duration seem to gain more by sinus surgery, which is something we need to look further at.

Background: Patients with uncontrolled CRS have persistent bothersome symptoms despite appropriate treatment with nasal corticosteroids and endoscopic sinus surgery. The aim of this study was to identify which T cell subtype of untreated, steroid naive CRSwNP and CRSsNP patients influences the disease control.

Methods: CRS was diagnosed based on symptoms, nasal endoscopy and CT scan. Sinonasal mucosa (uncinate process) or middle meatal polyp tissue were obtained from 31 untreated CRS patients (18 CRSwNP and 13 CRSsNP) and analyzed histopathologically and by flow cytometry. Patients were subsequently treated medically and if unresponsive surgically. The average follow up duration was 15.8 ± 4.6 months after tissue sampling. Patients with persistent symptoms on VAS ≥5 despite treatment represented the uncontrolled CRS group.

Results: The CRSwNP group had significantly more CD4+ cells then CRSsNP group (34.05±19.89 vs. 22.04±16.71, p=0.028) and significantly less CD8+ cells then CRSsNP group (25.97±7.57 vs. 31.07±12.33, p=0.002). All uncontrolled CRSwNP patients had tissue eosinophilia. In the well-controlled CRSwNP there were significantly more Th17 CD4+CCR6+ cells (13.28±5.96) than in the uncontrolled CRSwNP (7.16±4.89, p=0.046). In the uncontrolled CRSwNP there were significantly more
double negative T17 CD4-CD8-CCR6+ cells (12.20; 2.10) then in the well-controlled CRSwNP group there were significantly more cytotoxic CD3+CD8+ cells (79.8±7.8) then in the well-controlled CRSwNP group (52.95±28.17), p=0.045. In the well-controlled CRSwNP group there were significantly more double negative CD4-CD8- cells (46.93±28.29) then in the uncontrolled CRSwNP group (20.70±7.59), p=0.019.

Conclusions: By flow cytometry we were able to show the Th17 CD4+ CCR6+ cell to predict well-controlled CRSwNP; we could explain that by Th17 cell plasticity, being able to transform into Th1 cell. Double negative T17 CD4-CD8-CCR6+ cell (also capable of IL-17 production) predicted uncontrolled CRS; double negative T17 cells are known to promote immune cell recruitment and tissue immunoglobulin production in autoimmune diseases. In CRSwNP being cytotoxic type of inflammation the Th CD8+ cell predicted the uncontrolled disease. The double negative CD4-CD8- predicted the well-controlled CRSwNP which could be the result of CD8 silencing.

010 Relationship between the response to allergen, histamine and hypertonic saline nasal challenge and subjective reactivity to irritants in subjects with seasonal allergic rhinitis

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Background: Patients with seasonal allergic rhinitis (SAR) may have symptoms triggered by environmental changes and irritants exposure in the absence of allergen. It is hypothesized that level of hyperreactivity in mixed rhinitis is related to the inflammation in the late phase response, stimulation of sensory nerves and transient receptor potential (TRP) channels. The study was done to compare subjective and objective response to the low-dose allergen, histamine and hypertonic saline challenge, with subjective responsiveness to common irritants.

Methods: A group of 45 non-asthmatic patients with SAR, were submitted to consecutive nasal provocations, out of season, with 1.000 I. U. of allergen, 80 mcg of histamine 24 hours after allergen challenge, and 48 hours after histamine with 2% hypertonic saline (HTS). Prior to the challenges patients filled in a modified Cincinnati irritant index questionnaire testing subjective sensitivity to 20 common environmental triggers (scale 0-10). Before and after challenges visual analog scale (VAS) subjective scores of nasal and ocular symptoms, and nasal lavages were done 15 minutes after, and 24 hours after allergen, and 15 minutes after histamine and HTS. Nasal lavages were analysed for eosinophil cation protein (ECP) 4 and 24 hours after allergen and substance P (SP) 15 minutes after HTS challenge.

Results: Highest score for individual irritant in the Cincinnati irritant index scale (CIS) was found for cold air and tobacco smoke, followed by weather changes and cleaning solutio. Total score in CIS correlated significantly with differences in VAS prior to and after allergen challenge for buming sensation in the nose (rho 0.47, p=0.001) and eye itch (rho 0.49, p=0.0001). On the other hand, subjective responsiveness for cold air correlated with VAS difference for obstruction (rho 0.32, p=0.03), secretion (rho 0.33, p=0.03) and nose itch (0.38, p=0.008). There was no correlation between ECP and SP levels in lavages and sneezing count with subjective responsiveness to irritants (total CIS score).

Conclusions: Different patterns of symptoms after low-dose nasal challenges in patients with mixed rhinitis may be attributed to sensitivity to specific set of irritants. Severity of inflammation after such challenges does not reflect subjective irritant sensitivity. In patients with high subjective sensitivity to a broad panel of irritants, a psychosomatic component of multiple chemical sensitivity may be considered.

011 Influence of the diagnosis chronic rhinosinusitis on asthma response to omalizumab in severe, uncontrolled asthmatics

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Background: Omalizumab is a humanized anti-immunoglobulin E (IgE) monoclonal antibody that has been approved as add-on therapy for the treatment of adults with moderate-to-severe (United States) or severe (Europe) allergic asthma, inadequately controlled after treatment with high-dose inhaled corticosteroids plus long-acting ß-agonists. The clinical efficacy of Omalizumab has not only been shown in the treatment of severe uncontrolled asthma, but also in the treatment of nasal polyposis and comorbid asthma. The aim of this analysis was to examine whether the diagnosis of chronic rhinosinusitis (CRS) influenced the asthma response to Omalizumab treatment.

Methods: This study retrospectively analysed data from 70 patients with severe, uncontrolled asthma treated with Omalizumab. A skin prick test (SPT) was performed in all patients. In serum, specific Immunoglobulin E (IgE) to Staphylococcal enterotoxins (SE) and total IgE were measured by Immunocap. Asthma response was evaluated by physician’s Global Evaluation of Treatment Effectiveness (GETE-score); GETE 0, 1 and 2 were considered as non-responders, GETE 3 and 4 as responders.

Results: The mean age of the patients was 54.4 years and 62% of them were female. 84.3% of the asthmatics responded to Omalizumab with antibodies to SE and in patients with CRSwNP.

Conclusions: We here showed that a high proportion of severe uncontrolled asthma patients are sensitized to staphylococcal enterotoxins and more than half of these severe asthmatics have comorbid nasal polyposis. There is a trend towards a better asthma response in patients with antibodies to SE and in patients with CRSwNP.
Method: Epithelial cells were obtained from concha inferior biopsies of allergic rhinitis (AR), non-allergic rhinitis (NAR) and healthy controls. Affymetrix arrays and were used to determine the expression profiles.

Results: Comparing subgroups of NAR patients with healthy controls three significant differences were observed related to the activation state of genes. Two classes of genes were significantly up-regulated in non-allergic rhinitis. The first class is related to interferon (INF) signalling and the second class is related to epithelial growth factor receptor (EGFR) signalling pathway. Finally there was a significant difference in cold-induced RNA binding protein (CIRBP) that was activated in NAR and de-activated in healthy. These three path could well be related as CIRBP is able to affect ERK activity downstream of EGFR resulting in increased IFN-levels.

Conclusion: Assessing differences between chronic rhinitis subgroups using a completely unbiased approach has revealed a novel profile in non-allergic rhinitis. This profile seems linked to the way nasal airway epithelial cells respond to cold air. The last observation is very relevant because cold-dry air provocation is the golden standard to assess nasal hyperreactivity. The increased activity of the EGFR and INF-pathways in turn might well explain the symptomatology in these patients.

**P2**
Ivacaftor and sinonasal pathology in a cystic fibrosis patient with genotype delta F508/S1251N
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**Background:** Since the discovery of the cystic fibrosis (CF) gene in 1989, attempts have been made to develop a new therapeutic approach by targeting the underlying CFTR protein defect. Ivacaftor (Kalydeco®, Vertex Pharmaceuticals) is the first of a new class of drugs known as CFTR protein potentiators. This drug is functional in “CFTR gating” or type III mutations, in which a dysfunctional CFTR protein is present at the apical membrane. Ivacaftor facilitates improved chloride transport by increasing the opening time of the CFTR channel 1. Research has shown that treatment with ivacaftor can significantly improve lung function by about 10% [1]. Adverse events of ivacaftor include upper respiratory tract infections, nasal congestion and headaches [2].

**Case report:** In our case report we illustrate a positive effect of ivacaftor on the sinonasal pathology in a 17 year old patient with CF. Her CF genotype showed a heterozygous deltaF508/S1251N mutation, in which the S1251N mutation is a type III mutation and can therefore be influenced by ivacaftor. In addition to her pulmonary symptoms she chronically suffered from headaches and nasal obstruction, most likely caused by chronic rhinosinusitis. During these complaints two CT-sinuses were performed (fig. 1A and 1B), showing opacification of all paranasal sinuses. A new CT-sinus (fig. 1C) showed complete resolution of the opacification of the paranasal sinuses and a decrease in symptoms of sinonasal disease. This positive effect of ivacaftor on sinonasal pathology seems promising, therefore more research is needed to evaluate the effect of ivacaftor on the upper airways in CF.

**Consent:** Written informed consent was obtained from the patient for publication of this abstract and any accompanying images.

**References:**

**P3**
TAS2R38 taste receptor gene and chronic rhinosinusitis: a bitter ending
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Clinical and Translational Allergy 2015, 5(Suppl 4):P3

**Background:** Chronic rhinosinusitis (CRS) is a frequent disease with a high social impact and multifactorial pathogenesis. Recently, single nucleotide polymorphisms (SNPs) within the TAS2R38 gene were pointed at as possible contributors to the complex gene-environment interactions in CRS. This hypothesis was supported by in vitro evidence of the protective effect exerted by the functional bitter taste receptor T2R38 on sinonasal mucosa, due to its role in innate immunity. The purpose of this study was to confirm the proposed correlation between TAS2R38 genotype and CRS comorbidities and to assess whether the presence of a particular allele can be considered a prognostic marker.

**Methods:** Fifty-three CRS patients and thirty-nine healthy individuals were genotyped at the TAS2R38 locus. CRS patients were treated by endoscopic sinus surgery and medical therapies and subdivided in “recalcitrant” and “healed”, depending on the clinical outcome, assessed by internationally accepted scoring systems. Chi-square analyses were used to assess the effect of genotype on CRS and CRS-related comorbidities.

**Results:** The distribution of the different genotypes at the TAS2R38 locus was not significantly different between recalcitrant CRS patients, healed CRS patients and controls (χ² [10] = 2.75, p = 0.99). Besides, no associations were found between the different genotypes at the TAS2R38 locus and CRS-related comorbidities.

**Conclusions:** No association was found between TAS2R38 alleles or genotypes and CRS, thus questioning its real contribution to CRS susceptibility. Further studies on larger cohorts are needed to verify these findings also in vivo and to shed light on the role of bitter taste receptors in CRS.

**P4**
Breaking nasal epithelial cell tolerance lipopolysaccharide exposure by CD16 mediated co-stimulation with human serum immunoglobulin G
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**Background:** Nasal epithelial cells are the first line of defence against invading microbes. In everyday life, we are constantly exposed to variety of bacteria and viruses, but not every exposure leads to a development of pro-inflammatory responses of nasal epithelium. Although triggering of an individual PRR is known to induce cell responses, it has become clear that the ultimate profile of cytokines production strongly depends on the cross-talk between different receptors. We have previously shown that exposure of nasal epithelium to viruses enhances its responses to Gram-positive bacteria. Since pathogenic bacteria are commonly tolerated in the human nose, we sought to characterize the nasal epithelium responses to LPS, a major component of Gram-negative bacteria cell wall.

**Methods:** We exposed primary nasal epithelial isolated from 5 healthy individuals to TLR-4 agonist LPS (range:10 μg/mL to 10 μg/mL) and to human serum IgG (100 μg/mL), IgA (1 μg/mL), or IgE (1 μg/mL) in a time course over 24 hours. CD16, CD12, and CD64 receptors were blocked by preincubating the cells with 20 μg/mL of specific antibody for 30 minutes at 37°C. Expression of IL-6 and IL-8 was analysed by q-PCR and their production levels were determined by ELISA.

**Results:** Despite the presence of the LPS receptor complex (TLR-4, CD14, and MD-2), 24-hour exposure of nasal epithelium to LPS did not induce
IL-6 or IL-8 production at either mRNA or protein level. However, cell co-stimulation with IgG resulted in a 1.9 to 3.4 (p < 0.01) or 1.6 to 4.3 (p < 0.05) fold amplification of the IL-6 and IL-8 protein production respectively, depending on LPS concentration and inter-individual differences. In vivo, the enhancement was related to cell responses to LPS alone. At the mRNA level, synergistic responses were even more pronounced and enhanced IL-6 expression 2.6 to 13.2 fold (p < 0.05) and IL-8 by 2.2 to 15.0 fold (p < 0.05). Importantly, IgG itself did not induce cytokine production. Cell responses to LPS were not amplified by co-stimulation with IgA or IgE. Moreover, the IgG-enhanced cell responses to LPS were abrogated to LPS-alone induction levels of IL-6 and IL-8 after blocking the CD16 (p < 0.05), but not CD32 or CD64 receptors.

Conclusion: The data demonstrate that LPS-induced cytokine production by nasal epithelium is more complex than previously considered and show that the cross-talk of CD16 and TLR-4 may be important for the induction of Gram-negative bacteria specific immunity.

**P5** Nasal cytology: a new diagnostic approach in rhinoLOGY
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Clinical and Translational Allergy 2015, 5(Suppl 4):P5

Nasal cytology is a diagnostic method in the field of rhinology used to detect changes in the endonasal epithelium exposed to physical and/or chemical irritation, acute or chronic inflammation due to different agents (viral, bacterial, fungal or parasitic). Nasal cytology was born in 1889 thanks to H. Gollasch who found many eosinophilic cells into the nasal secretions of a patient affected by asthma, and thought of them as important elements in the pathogenesis of this disease. The main evolution of nasal cytology occurred in 1927, thanks to the report done by C. Eyermann, who noted the presence of eosinophilic cells into the nasal secretions of allergic patients. Since then great importance is given to the recognition of specific cell types into the pathogenesis of different nasal diseases. Nasal cytology is nowadays more frequently used in the study of allergic, vasomotor, inflammatory and infectious rhinitis. It is a simple, non-invasive and repeatable examination which is useful in the follow-up and monitoring of the real effectiveness of medical and surgical treatments. Patients affected by allergic rhinitis (AR) develop an endonasal immediate response, so-called "early phase", followed by a "late phase" response to the allergenic agent. From the microscopic point of view, both these responses are always characterized by an infiltration of the mucosa by immunoflogistic cells (eosinophils, mast cells, neutrophils and lymphocytes) that, following the release of several chemical mediators, are the main cause of the symptoms that characterize the IgE-mediated disease. In AR the main cells type released during the immunological response will change depending on whether the patient is examined during or outside the pollinic season. In the first condition, the patient will present all the clinical signs and his nasal cytology examination will be characterized by neutrophils, lymphocytes, eosinophils and mast cells largely degranulated. Nasal cytology allows us to differentiate between various forms of rhinitis which are resumed as: non-allergic rhinitis with neutrophil (Narne); non-allergic rhinitis with eosinophilia (NARES); non-allergic rhinitis with mast cells (NARMA); non-allergic eosino.

**UPPER AIRWAY - INFLAMMATORY MECHANISMS (INNATE/ADAPTIVE)**

**P7** Converging evidence for the pro-inflammatory role of p-glycoprotein in Th2 polarized chronic rhinosinusitis endotypes
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Clinical and Translational Allergy 2015, 5(Suppl 4):P7

Background: T-helper 2 (Th2) inflammation is a hallmark of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and eosinophilic CRS (eCRS) although the pathogenesis is poorly understood. P-glycoprotein (P-gp) is an efflux pump which is expressed within sinonasal mucosa and is capable of regulating cytokine transport in both epithelial and T-cells. The purpose of this study was to synthesize multiple lines of evidence suggesting that P-gp may promote inflammation in Th2 polarized CRS endotypes.

Methods: The findings of 8 prior studies (5 in vitro and 3 clinical) by our research consortium were examined for the presence of a consistent mechanistic framework linking the presence of altered P-gp expression and function to enhanced Th2 inflammation.

Results: Two studies performed in primary epithelial cell culture demonstrated that P-gp expression is responsive to TLR4 stimulation and modulates Th2 cytokine secretion. These findings were replicated in 2 organotypic nasal polyp explant studies which demonstrated that the secretion of IL-5 and TSLP was highly correlated with P-gp expression and could be blocked using the P-gp inhibitors Verapamil or Zosuquidar. Three complimentary clinical studies demonstrated that P-gp was specifically overexpressed in polyp tissue and that expression correlated with tissue eosinophilia, Lund-Mackay Scores, and Kennedy Osteitis scores. A final in vitro study demonstrated that ClariThromycin and Itraconazole possess occult P-gp inhibitory properties.

Conclusion: Multiple lines of evidence suggest that P-gp regulates the secretion of Th2 polarizing cytokines from its host cell. Furthermore, the concentration of secretion is strongly correlated with the level of P-gp expression indicating a direct pro-secretory role. The P-gp overexpression found in CRSwNP and eCRS may therefore be interpreted as playing a central role in the maintenance of Th2 inflammation through enhanced cytokine secretion. The anti-P-gp effects of ClariThromycin and Itraconazole, two drugs with known anti-inflammatory properties, hint at a possible novel therapeutic strategy mediated by P-gp inhibition.
mposerant* (a novel intranasal formulation of azelastine hydrochloride [AZ] and fluticasone propionate [FP]) has demonstrated significant clinical effects in AR compared to these drugs in monotherapy. The aim of this study was to investigate the anti-inflammatory effect of MP29-02* compared to AZ and FP alone in an in vitro validated model of eosinophilic inflammation.

**Methods:** Peripheral blood eosinophils were incubated for 4 days with decreasing dilutions of MP29-02* (from 1:10 to 1:100000, equivalent dilutions of FP (7.3x10^6 M to 10^3 M) or AZ (2.4x10^6 M to 10^3 M) prior to the addition of Epithelial Cell culture Media (ECM) from nasal mucosa (NM). Eosinophil survival was assessed by Trypan blue dye exclusion. Results are expressed as percentage (mean ± SEM) of eosinophil survival compared to control (100%).

**Results:** ECM from NM at 10% induced eosinophil survival from day 1 to 4. This effect was inhibited in a dose-response manner by MP29-02* and FP alone (from day 2 to 4) and AZ alone (only at day 4). At day 3, MP29-02* significantly inhibited eosinophil survival induced by ECM from dilution 1:10 (13±1.5%, N=6) to dilution 1:100 (58±8.8%, N=6), compared to ECM (100%). This inhibitory effect on eosinophil survival induced by MP29-02* at 1:10 dilution (13±1.5%) was significantly (p<0.05) stronger than that induced by FP alone (36.7±6.3) or AZ alone (70.3±10.4%) at similar dilutions.

**Conclusions:** These results suggest that MP29-02* may reduce upper airway eosinophilic infiltration more potently than corticosteroids or antihistamines administered alone. This anti-inflammatory effect may account, at least in part, for the stronger clinical effect of MP29-02* on moderate to severe allergic rhinitis when compared to these drugs in monotherapy. This study has been sponsored by a research grant from MEDA Pharma. * Dymista.

**P17 The effect of MP29-02* is mediated via bitter taste receptors (TAS2R) with an advanced delivery system with a well-documented effect on allergic**

**Background:** Recently, MP29-02* (a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP)) in an advanced delivery system with a well-documented effect on allergic

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**Acknowledgement:** Supported by Comenius University Grant No. UK/120/2014.
rhinitis. Its somewhat bitter taste is probably derived from AZE, a potent histamine-H1-receptor antagonist. The taste is sometimes looked upon as a disadvantage. However, it might be that AZE induces some of its beneficial effect through activation of bitter taste receptors. Recent evidence indicates that bitter taste receptors are present in human upper airway mucosa in regions associated with high airflow and particulate deposition. Consequently the MP29-02* effects might be due not only to its anti-histaminic, mast-cell stabilizing, anti-leukotriene, and anti-inflammatory properties but also as due to activation of bitter taste receptors.

Aim: To explore if MP29-02* has the ability to activate bitter taste receptors using an in-vitro model of isolated murine airways and to probe the potential bitter taste effects of MP29-02* on human nasal epithelial cells.

Methods: Bitter taste receptor activation was investigated in isolated murine airways incubated in tissue baths. Balb/c mice (male) were used since they are known to have a weak histamine receptor system. MP29-02*, AZE and FP were added cumulatively to tracheal segments pre-contracted with Carbachol. Primary human nasal epithelial cell were cultured in the presence of different concentrations of MP29-02*, AZE and Chloroquine (a bitter taste TAS2R agonist) and evaluated in relation to traditional activation markers, such as VCAM-1 and CD86.

Results and comments: MP29-02* is a potent dilator of pre-contracted airways, an effect probably mediated by its AZE component. The obtained results make it clear that this is not the result of histamine receptor activation. The relaxant response of MP29-02* and AZE mimics the response induced by the bitter taste TAS2R agonist, Chloroquine. The mechanisms behind bitter taste receptor mediated relaxations are not yet known. The presented experiments rule out the involvement of prostaglandins, cAMP and cGMP (all known to be common pathways for airway dilation) for both MP29-02* and Chloroquine. Furthermore, preliminary data indicate that Dymista® has the ability to trigger nasal epithelia cells in a way that resembles of the effects induced by Azelastin and Chloroquine. There are no known antagonists for bitter taste receptor, but taken together, the presented data supports our notion that MP29-02* is a potent bitter taste agonist, which may contribute to its superior efficacy over AZE and FP observed in clinical trials.

* Dymista.

UPPER AIRWAY - PHENOTYPE AND ENDOTYPES

P19 Immunologic responses to the major allergen of Olea Europaea in local and systemic allergic rhinitis subjects

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Clinical and Translational Allergy 2015, 5(Suppl 4):P19

Background: Ole e 1 is one of the major allergens from olive tree pollen. Up to date there are no specific studies that evaluate in depth the in vitro responses to this purified allergen. The goal of the study was to thoroughly evaluate the cellular responses to nOle e 1 in allergic rhinitis (AR) and local allergic rhinitis (LAR) patients with sensitization to olive tree pollen (OL) demonstrated by nasal allergen provocation test (NAPT).

Methods: Twelve subjects with AR (+NAPT with OL, + skin testing and specific IgE (sIgE) to OL), 12 subjects with LAR (+ NAPT with OL, - skin testing and sIgE to OL), and 12 subjects as control group (CG) (- NAPT, - skin testing and sIgE to OL) were selected. Basophil activation tests (BAT) with OL and nOle e 1, along with dendritic cell (DC) maturation/proliferation studies in response to nOle e 1 stimulation, were carried out in all subjects. Local ethical committee approved the study.

Results: All AR subjects had positive BAT responses to OL and 10/12 to nOle e 1 (83%); 8/12 LAR (66.6%) had a positive BAT with OL and 4/12 (33%) to nOle e 1, with only one subject of the control group with a positive BAT to both OL and nOle e 1 (8%). DC proliferation and maturation were increased in SAR>LAR>CG but with no significant differences (maturation: 66.7%/57%/0%; proliferation: 40%/20%/0%).

Conclusion: BAT with OL and nOle e 1 in LAR group showed sensitivity between 66.6 and 33%, demonstrating specific basophil activation with pollens in patients with LAR. DC proliferation and maturation were demonstrated in SAR and LAR subjects although with no significant differences with CG.

P20 Proprotein convertase 5/6A is associated with bone morphogenetic protein-2-induced squamous cell differentiation

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Background: Squamous metaplasia in airway epithelium is a pathological process arising from abnormal remodeling/repair responses to injury. Proteolytic maturation of many growth and differentiation factors
involved in tissue remodeling is controlled by proprotein convertases (PCs). However, the role of these convertases in airway remodeling remains poorly understood.

**Method:** Expression of differentiation markers and PCs was determined in human nasal epithelial cells (HNECs) cultured at the air-liquid interface (ALI). Histologic analysis and immunohistochemistry for PCs and bone morphogenetic protein-2 (BMP-2) were performed in ALI cultures, and with Normal human nasal mucosa and nasal polyps.

**Results:** Using a retinoic acid deficiency-induced squamous metaplasia model of HNECs, we observed a significant increase in the expression of PCs/6A, a PC member, and BMP-2, a candidate substrate for PCs/6A. Specific lentiviral shRNA-mediated PCs/6A knockdown decreased BMP-2 expression and maturation, decreased expression of squamous cell markers, and increased expression of ciliated cell markers. Dec-RVKR-CMK, a PC inhibitor, and LDN-193189, a BMP receptor inhibitor, suppressed squamous differentiation, promoted mucociliary differentiation, and down-regulated the BMP-2/Smad1/5/8/p38 signalling pathways. Dec-RVKR-CMK also decreased expression of PCs/6A, but not furin, another PC member, suggesting the involvement of PCs/6A in squamous differentiation of HNECs. Overexpression of PCs/6A and BMP-2 in the human nasal epithelial cell line RPMI-2650 demonstrated that PCs/6A can activate BMP-2. Under retinoic acid-sufficient culture conditions for multiple histologies of differentiation of HNECs, short-term expression of PCs/6A by the adenovirus system and addition of exogenous BMP-2 induced squamous differentiation. Furthermore, PCs/6A and BMP-2 were highly expressed in metaplastic squamous epithelium of human nasal polyps.

**Conclusion:** Taken together, PCs/6A is involved in squamous differentiation of HNECs, possibly through up-regulation of the BMP-2/Smad1/5/8/p38 signalling pathway, pointing to a potential therapeutic target for the prevention of chronic airway diseases that exhibit squamous metaplasia.

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**P24**

*Heredity, symptoms and risk factors of nasal polyps*

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**Clinical and Translational Allergy 2015, 5(Suppl 4):924**

**Background:** The aim of this study was to investigate the heredity of nasal polyps and study the symptoms and risk factors of patients with this condition.

**Method:** Patients with nasal polyps were recruited from the clinic, adult first-degree relatives of the patients were asked to participate. Our intention was to recruit one relative of each gender per patient. All participants were examined with nasal endoscopy and underwent a structured interview regarding upper airway symptoms and risk factors. The results were compared with a general population from a previous study who had been examined and questioned in the same way.

**Results:** 368 patients and 410 relatives were recruited. A control group, consisting of 1387 individuals from the general population, was used for comparison. The prevalence of nasal polyps among the relatives was 13.4%, which was almost five times higher than the prevalence in the control group (2.7%). The prevalence of nasal polyps within the families was 19.2%. The symptoms and risk factors associated with nasal polyps were nasal secretions, nasal blockage, sneezing and impaired sense of smell. Male sex, increasing age and asthma were also associated with the disease. Smoking was not a risk factor in this study.

**Conclusion:** The results of this study strongly indicate that heredity is important in the development of nasal polyps. We are currently investigating possible genetic polymorphisms associated with nasal polyps in a genome-wide association study. Nasal secretions, nasal blockage, sneezing, impaired sense of smell, male sex, increasing age and asthma are symptoms and risk factors associated with nasal polyps.

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**P21**

*Poaceae molecular sensitization profile in selected rhinitis patients with allergy to grass pollen and maize-derived edible products*

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**Clinical and Translational Allergy 2015, 5(Suppl 4):921**

**Background:** Clinical cases of allergic reactions induced by ingestion of maize-derived products have been rarely published, and most patients with food allergy to *Zea mays*, from the *Panicoideae* subfamily, are also sensitized against pollen of the *Poaceae* subfamily grasses, belonging to the same *Poaceae* family.

**Methods:** Patients from Southern Romania with grass pollen rhinitis, diagnosed by allergy evaluation with positive skin prick tests and high serum levels of specific IgE to *Poaceae* pollen, were screened for food allergy by detailed clinical history of symptoms related to maize-derived edible products, including foods with corn as basic ingredient, such as polenta, porridge, cornflakes, tortilla chips, popcorn, canned kernels, or traditional products, such as stigmas and corncob leaves with pollen deposition. Patients with occupational exposure to maize flour or pollen were not included, and ceremonial use of oral corn pollen in the Romanian Plain was not reported. We assessed the IgE sensitization profile to pollen allergen components used as biomarkers of *Poaceae* allergy by a novel multiparameter immuno blot test system.

**Results:** Two adult allergic rhinitis patients were selected, one woman with history of oral allergy syndrome to polenta and tortilla chips and a man with urticaria after ingesting *Stigma maydis* infusion. Regarding the group 1 beta-expansins, with role in pollen tube penetration, and the group 12 profilin panallergens, important allergen components present in kernels and pollen, both patients had high levels of serum specific IgE to *Poaceae* pollen, were screened for food allergy by detailed clinical history of symptoms related to maize-derived edible products, including foods with corn as basic ingredient, such as polenta, porridge, cornflakes, tortilla chips, popcorn, canned kernels, or traditional products, such as stigmas and corncob leaves with pollen deposition. Patients with occupational exposure to maize flour or pollen were not included, and ceremonial use of oral corn pollen in the Romanian Plain was not reported. We assessed the IgE sensitization profile to pollen allergen components used as biomarkers of *Poaceae* allergy by a novel multiparameter immuno blot test system.

**Conclusion:** Some pollen grain protein allergen components have good thermostability, maize polcalcin being probably involved in allergy to infusion of herbal products containing stigmas receiving pollen, while profilins possibly not, being more sensitive to heat denaturation. Maize beta-expansin 11, a Phl p 1 homologue, may have a high cross-reactive potential in patients who suffer both from food allergy and grass pollinosis. Interestingly, patients were not sensitized to grass pollen allergens, molecular components not representative in corn pollen.

**Consent:** Written informed consent was obtained from the patient for publication of this abstract and any accompanying images.

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**P26**

*Acute and chronic rhinosinusitis and allergic rhinitis in relation to environment, comorbidity and ethnicity*

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**Clinical and Translational Allergy 2015, 5(Suppl 4):926**

**Aims:** This study was conducted to assess the relation between allergic rhinitis (AR), acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) and environment, comorbidity and ethnicity.

**Methods:** A posted GA2LEN screening questionnaire was sent to all those in a random sample of Dutch population (n=16700) in three different areas.

**Results:** The prevalence of ARS is significantly related to AR, a doctor’s diagnosis of CRS, urticaria, eczema, smoking, gender, ethnicity and age. The prevalence of CRS is significantly related to AR, a doctor’s diagnosis of CRS, urticaria, adverse response to painkiller, smoking, ethnicity, asthma and age. The prevalence of AR is significantly related to a doctor’s diagnosis of CRS, urticaria, eczema, adverse response to painkiller, smoking, occupation, ethnicity, asthma, age, CRS and AR.

**Conclusion:** Some environmental factors, comorbidity and ethnicity are positively or negatively related to AR, ARS and CRS. Place of residence in the Netherlands is not related to the prevalence of these diseases.
P27
Chronic rhinosinusitis in adolescence is a rare but bothersome condition - data from a Swedish population based cohort
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Clinical and Translational Allergy 2015, 5(Suppl 4) P27

Background: Symptoms of chronic rhinosinusitis (CRS) is common, around 10% among adults, and has shown to be associated with reduced quality of life. No study has focused on adolescents specifically. Therefore, we wanted to estimate the prevalence of CRS in adolescence and evaluate the burden of symptoms.

Method: We used 3112 16-year-olds from a Swedish birth cohort called BAMSE. The adolescents who fulfilled the criteria of CRS according to the European Position Paper on Rhinosinusitis (EPOS) in a questionnaire, was contacted by telephone to verify the diagnosis. Those with ongoing symptoms were invited for a clinical follow up with nasal endoscopy, olfactory threshold test (Sniffin’ Sticks) and the disease specific quality-of-life (QoL) questionnaire SNOT-22 (Sino Nasal Outcome Test 22). QoL was compared to those without CRS with the generic EQ-5D VAS.

Results: Among the 3112 16-year-olds 43.5% reported symptoms from the upper airways during the last 12 months, but only 1.5% (n=48) reported symptoms of CRS. 27 of the 48 adolescents still had ongoing symptoms of CRS at the telephone interview. At clinical examination of 23 of the 27 adolescents, 22 still fulfilled the criteria of CRS among whom 9 had endoscopic signs of CRS, corresponding to a prevalence of 0.3%. The 22 adolescents with symptoms of CRS more often had allergic rhinitis symptoms (57.1% vs 28.1%, p=0.003) asthma (25.0% vs 11.0%, p=0.047) and cough ≥ 3 months (13.6% vs 3.4%, p=0.008) compared to those without symptoms of CRS. The median EQ-5D VAS score was lower compared to the rest of the population (Mdn=80 vs Mdn=90, p=0.024). The mean SNOT-22 value was 38.2 among the 22 adolescents with symptoms of CRS and 44.2 among the 9 adolescents with endoscopic signs of CRS. The corresponding mean values for the olfactory threshold were 6.08 and 6.33, respectively.

Conclusion: At adolescence CRS exists even though the prevalence is low, between 0.3% and 1.5%. Those affected have a significantly reduced quality of life.

P28
Patient reported outcome measurements in chronic rhinosinusitis; assessing the correlation between RSOM-31 and VAS
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Clinical and Translational Allergy 2015, 5(Suppl 4) P28

Background: Quality of Life (QoL) questionnaires are probably the most reliable outcome measurements to measure control of disease in CRS but can be relatively cumbersome. In certain situations a VAS (Visual Analogue Score) asking patients how their CRS is in general might be an easier evaluation tool.

Aim: In this study we analyse the correlation between the RSOM-31 questionnaire, a VAS overall sinus’ score, and the comparable items measured as VAS.

Methods: We collected RSOM-31, ‘VAS overall sinus’ score and VAS per symptom and analysed correlations.

Results: 705 CRS patients were included in this study (CRS-I = 300). Correlation between mean RSOM-31 and ‘VAS overall sinus’ score showed a moderate correlation (r=0.52), as did the correlation between RSOM-31 nasal domain and ‘VAS overall sinus’ score (r=0.52). Excellent correlations between RSOM-31 and VAS were found for the comparable symptom specific questions; nasal congestion (r=0.80), rhinorhea (r=0.83), sneezing (r=0.81), impaired sense of smell (r=0.82) and postnasal drip (r=0.86), all p-values <0.001. None of the individual RSOM-31 items correlated well with the VAS overall sinus’ score.

Conclusion: We found a moderate correlation between mean RSOM-31 or RSOM-31 nasal domain and ‘VAS overall sinus’ score. The moderate correlation between these scores suggests patients, in both instruments, reflect different aspects of the burden of their disease. Further studies are needed to determine what patients include in their overall VAS score that is not captured with RSOM-31.

CLINICAL RHINOLOGY - ALLERGEN IMMUNOTHERAPY

P29
Intralymphatic Immunotherapy (ILIT) with both grass and birch allergens - a randomized controlled trial
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Clinical and Translational Allergy 2015, 5(Suppl 4) P29

Background: Allergen specific immunotherapy is an effective treatment of allergic rhinitis. It is most commonly administered as repeated subcutaneous injections or as a daily sublingual tablet during 3-5 years. In order to shorten the treatment duration previous studies have evaluated the use of intralymphatic injections (ILIT) with promising results. This study assesses safety and efficacy of ILIT with two allergens given simultaneously.

Method: 60 patients 2012-2014 with moderate to severe birch and mild to moderate grass pollen allergy were recruited. They were randomized 1:1 to three ultrasound guided intralymphatic injections with placebo or ALK Alutard Birch and Grass 1000 SQU in each groin with one-month interval. The quality of life was assessed at peak pollen season using the rhinitis related quality of life (QoL) questionnaire Sinonasal Outcome test (SNOT-22). Allergen specific IgE and IgG4 were monitored and flow cytometry was used to characterize blood and lymph node aspirate.

Results: 36 patients have been analyzed so far (data from 2012-13). 14 patients received active treatment and 22 placebo. Baseline characteristics including disease severity and QoL were the same in both groups. All side effects reported were mild; 8% of active patients had local swelling at injection site. In the placebo group the QoL scores worsened during peak birch season (mean of difference between off and during season: 19.70: 4.60, n=20, p=0.0004). In contrast, the scores remained unchanged in the active group (6.27±4.72, n=11, p=0.21). S-Birch IgG4 levels increased 2 weeks after active ILIT (mean difference 0.26±0.11 mg/L, p=0.04, n=11). No such change was seen after placebo (0.02±0.02 mg/L, p=0.97, n=17). S-Birch IgE levels increased 6-9 months after treatment in the active group (mean difference 12.05±14.8 KU/ml, p=0.02, n=12) but not in the placebo group (0.05±1.5 KU/ml, p=0.99, n=21). Th1 cells (indicated as CCR5+CD4+ cells) increased in blood after active ILIT (4.0±1.1%, p=0.04) but not after placebo (0.6±0.7, p=0.44). These cells also tended to increase in the lymph node. Memory T-cells in blood also increased following active treatment (p=0.05).

Conclusion: ILIT targeting birch and grass simultaneously appears to be a safe procedure. The treatment improves the quality of life during pollen season. This supports the idea of ILIT as an effective alternative route for specific immunotherapy.

CLINICAL RHINOLOGY - MEDICAL TREATMENT

P33
A new allergic rhinitis therapy (MP29-02*) provides effective and rapid symptom relief for patients who suffer most from the bothersome symptoms of nasal congestion or ocular itch
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Overall, MP29-02* patients showed greater reduction in rT7SS due fluticasone propionate [FP] in an advanced delivery system) in seasonal AR (SAR) patients presenting with nasal congestion or ocular itch predominantly compared to AZE, FP or placebo (PLA) nasal sprays.

Methods: 610 patients (≥12 yrs old) with moderate/severe SAR were randomized into a double-blind, PLA-controlled, 14-day, parallel-group trial to MP29-02*, AZE FP or PLA nasal sprays (all 1 spray/nostril bid [total daily doses: AZE 548μg; FP 200μg]). Patients were categorized as nasal congestion- or ocular itch-predominant (for those patients with baseline rT0SS ≥ 8) according to maximal symptom scores at baseline. Targeted symptom reduction was assessed for each predominant symptom over the entire 14 day period and on each day.

Results: Congestion-predominant MP29-02*-patients experienced 3 times the congestion relief of FP-patients (p=0.0018) and 5 times the relief provided by AZE (p=0.0001). AZE and FP did not significantly differ from PLA. Superior congestion relief afforded by MP29-02* in these patients was evident from Day 2 vs FP (p=0.0155), AZE (p=0.0032) and PLA (p=0.0010) and sustained for 14 days. The level of relief achieved by MP29-02* patients on Day 2 (-0.90) was not achieved before Day 9 by either FP or AZE patients. Ocular itch predominant MP29-02*-patients experienced 4 times the ocular itch relief as FP-patients (p=0.0026) and twice the relief provided by AZE (p=0.0051). FP did not provide additional ocular itch relief over the placebo response. The level of ocular itch relief achieved by MP29-02* patients on Day 2 (-0.93) was not achieved before Day 9 by FP patients or before Day 4 by AZE patients.

Conclusion: Unlike currently available first line therapy, MP29-02* effectively and rapidly reduced nasal congestion and ocular itch in patients suffering predominantly from these symptoms. MP29-02*’s rapidity and effectiveness in relieving predominant congestion and ocular itch could lead to a reduction in the need for concomitant decongestants and eye drops, respectively and further supports the position of MP29-02* as the drug of choice for the treatment of AR.

* Dymista.

Reference

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P34
A new allergic rhinitis therapy (MP29-02*) provides nasal and ocular symptom relief days faster than current frontline monotherapies

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Background: The efficacy of MP29-02* (a novel intranasal formulation of azelastine hydrochloride [AZE] and fluticasone propionate [FP]) in an advanced delivery system) in providing overall nasal and ocular symptom relief vs AZE, FP or placebo (PLA) has been assessed.

Methods: Six hundred and ten moderate-to-severe SAR patients (≥12 yrs) were randomized into a double-blind, PLA-controlled, 14-day, parallel-group trial (NCT00660517) to MP29-02*, AZE, FP or PLA nasal sprays (1 spray/nostril bd; daily dose: AZE=548μg; FP=200μg). [1]. Change from baseline (CFB) in reflective total of 7 symptom scores (rT7SS; AM + PM, max=42) was assessed post-hoc. CFB in rT7SS and each nasal (congestion, itching, rhinorrea, sneezing) and ocular symptom (itching, redness, watering; max=6 each) was assessed over time.

Results: Overall, MP29-02* patients showed greater reduction in rT7SS vs FP, AZE & PLA (relative diff: 52% to FP (p=0.0013), 56% to AZE (p=0.0004); evident from treatment day 1 vs FP (p=0.0072), AZE (p=0.0336) or PLA (p<0.0001) and sustained for 14 days. The level of relief achieved by MP29-02* patients on Day 2 (-5.52) was not achieved before Day 5 by FP patients or Day 8 by AZE patients. This pattern of rapid, sustained and superior symptom relief by MP29-02* was observed for each nasal and ocular symptom, which was not the case with FP and AZE. MP29-02* provided significantly superior nasal congestion symptom relief than FP or AZE from Day 2; the level of congestion relief provided by MP29-02* on Day 2 (-0.77) was not achieved before Day 6 and Day 9 for FP and AZE, respectively. MP29-02* provided significantly superior ocular itching relief vs FP from Day 2 and vs AZE from Day 3; the ocular itch relief provided by MP29-02* on Day 2 (-0.77) was not achieved before Day 10 for FP-patients. Similarly, the level of ocular itch relief provided by MP29-02* on Day 3 (-1.06) was not achieved by AZE-patients before Day 11.

Conclusion: The consistent and rapid effect in alleviating all nasal and ocular symptoms is unique to MP29-02* and contributes to its superiority over AZE and FP. The time advantage over firstline therapy in achieving significant relief and sustained effect should improve patient concordance.

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Adenoidal enlargements and associated disease in children

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Introduction: Adenoid enlargement in the pediatric population is a common disease in the pediatric ENT field. Nasopharyngeal airway obstruction by adenoidal tissue was studied in children with otitis media with effusion, chronic suppurative otitis media, 32 with allergic rhinitis, 14 with the predominant symptoms chronic cough all of whom were scheduled for adenoidectomy. We preoperatively performed the following: nasal obstruction, mouth breathing, close rhinolalia, degree of hearing loss, level of IgE, and type of cough. We preoperatively performed fiber optic examination of the adenoidal tissue in nasopharynx in selected cases.

Results: All the patients in whom we performed adenoidectomy were evaluated 6 months later to appreciate the evolution of the associated disease. In 64% of patients with serous otitis media the aspects of tympanic membrane were normal, cough disappeared in 76% of the patients, and acute episode of rhinosinusitis were without recurrence. The patients with allergic rhinitis after adenoidectomy suffered from repeated or persistent episodes of hearing loss according to nasal obstruction and congestion from allergies.

Conclusion: Adenoidectomy in children is performed after general criteria, the history of the medical disease being very important, the incidence of acute episodes and recurrence of different types of infection in ENT field, without a possibility to establish the most important symptom relief vs AZE, FP or placebo (PLA) has been assessed.

which is individual. In the age group between 3 and 6 years, serous otitis media is predominant as is oral breathing. Rhinosinusitis appear to be more predominant in the age group between 6 and 10 years. We cannot establish a relationship between the dimension of adenoidal tissue and associated disease, but, associated diseases like allergic rhinitis have an important prognostic role.
Background: Four previously published trials assessed the efficacy of MP29-02* (a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) in an advanced delivery system) in seasonal allergic rhinitis (SAR) [1,2]. The first study compared MP29-02* to marketed AZE and FP (2). The others compared MP29-02* to AZE and FP in the MP29-02* vehicle and delivery device (i.e. re-formulated comparators) [1]. FP contained within MP29-02* has a unique PK fingerprint [3]. The aim of this analysis was to demonstrate that formulation/device contribute to MP29-02*’s clinical efficacy.

Methods: Four thousand and two moderate/severe SAR patients (≥ 12 yrs) were randomized into 4 double-blind, placebo (PLA)-controlled trials. Each trial comprised 4 groups: MP29-02*, AZE, FP and PLA nasal sprays, and was conducted for 14 days. Total daily dose of AZE and FP were 548 µg and 200 µg, respectively. Change from baseline (CFB) in reflective total nasal symptom score (rTNSS) over 14-days was the primary outcome. CFB in reflective total ocular symptom score (rTOSS) and individual nasal and ocular symptoms was assessed secondarily. Time to achieve at least a 50% rTNSS reduction from baseline was assessed post-hoc by Kaplan Meier estimates and log rank tests. The formulation/device effect of MP29-02* was quantified by comparing treatment differences obtained with MP29-02* vs marketed FP and MP29-02* vs re-formulated FP for these endpoints.

Results: For all efficacy variables assessed, the treatment difference was greater for MP29-02* vs marketed-FP than for MP29-02* vs re-formulated-FP. For rTNSS, the difference between MP29-02* and marketed-FP was -1.47, compared to -0.76 vs re-formulated-FP; a formulation/device effect of 0.71. Similarly for rTOSS a formulation/device effect of 0.70 was observed. A formulation/device effect was observed for relief of all individual nasal and ocular symptoms (e.g. 0.23 effect for congestion; 0.34 effect for ocular itching). Finally, MP29-02*-patients achieved a ≥50% rTNSS reduction ≤6 days faster than marketed-FP and ≤3 days faster than reformulated-FP, a formulation/device effect of ≤3 days.

Conclusion: Formulation and device contribute to MP29-02*’s superior efficacy over currently considered first-line therapy, making MP29-02* a new class of treatment for AR.

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References
parallel-group trials to MP29-02*, AZE, FP or PLA nasal sprays (1 spray/nostril bid), during the Texas mountain cedar (MP4001), Spring (MP4002), Autumn (MP4004) and Spring/Summer (MP4006) seasons. Overall change from baseline (CFB) in reflective total nasal symptom score (rTNSS) was the primary endpoint. It was assessed by severity post-hoc in 2 ways (more severe AR: median baseline rTNSS >18.9 or median baseline RQLQ >3.9; less severe AR: median baseline rTNSS ≤18.9 or median baseline RQLQ ≤3.9). CFB in individual nasal and ocular symptom scores was also assessed.

Results: The response to MP29-02* was consistent across seasons; mean CFB (5.5–5.6 and 6 in each study vs p=0.001 vs PLA). Nasal symptom relief was significantly greater with MP29-02* than with FP or AZE in all studies. In study MP4001 MP29-02 was approx. twice as effective as FP (relative difference (RD) 47%; p=0.0031) and 3 times as effective as AZE (RD: 66%; p<0.0001). For less severe AR (defined by median baseline rTNSS) the RD to MP29-02* was 42% vs FP (p=0.0188) and 64% vs AZE (p=0.0002), increasing to 49% and 70% vs FP (p=0.0046) and AZE (p=0.0035), respectively for more severe AR. When severity was categorized according to median baseline RQLQ the RD to MP29-02* was 60% vs FP (p=0.0244) and 69% vs AZE (p=0.0068) for those with less severe AR compared to 49% vs FP (p=0.0194) and 64% vs AZE (p=0.0013) for those with more severe AR. MP29-02* provided superior relief from all nasal and ocular symptoms than AZE or FP, which was particularly evident for congestion (p=0.0034 vs FP; p=0.0001 vs AZE) & ocular itching (p=0.0240 vs FP; p=0.0033 vs AZE).

Conclusion: MP29-02* provides consistently superior symptomatic relief to an intranasal antihistamine or topical corticosteroid in AR patients regardless of season, symptom or severity, supporting MP29-02* as the drug of choice for AR.

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P39
Identification of gaps in the current allergic rhinitis guidelines and how these can be filled
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Currently, there are gaps in the allergic rhinitis (AR) guidelines (and the evidence upon which they are based) that impede their function. Firstly, there is a high quality evidence supporting AR treatment decisions [1]. Randomized controlled trials (RCTs) often fail to compare active treatments and use endpoints that are regulatory (not patient) driven. Secondly, a common AR control language for both patients and physicians and a common concept of AR control is missing. Finally, to date, the guidelines do not draw on evidence from real-life studies. These are important as they determine the effects of treatment under the usual conditions of care, thus maximizing applicability of findings to everyday practice. Many of these gaps are currently being filled. Firstly, the efficacy and safety of MP29-02* (a novel intranasal formulation ofazelastine hydrochloride and fluticasone propionate in an advanced delivery system) has been shown versus active comparators in large, good quality, RCTs (2,3). MP29-02*’s superiority over currently considered gold standard therapy (INS) was assessed using more clinically-relevant efficacy endpoints, defining treatment response in a way that is understandable and relevant to patients and health care providers, helping to explain why current first-line therapy often provides sub-optimal symptom relief. Secondly, a simple visual analog scale (VAS) has recently been proposed by MACVIA-LR to depict the control language of AR. This will form the basis for the new AR guidelines as part of an integrated care pathway (ICP) [4]. This VAS is also an integral component of a new app called Allergy Diary, designed to assess and track disease control. AR control has been categorized using VAS cut-off scores as ‘well-, partly- and uncontrolled’. Finally, real-life studies are slowly gaining acceptance. One such study recently showed effective and rapid symptom control by MP29-02* in AR patients in real-life, using the same VAS score advocated in the ICP. Filling these gaps will ensure that treatment decisions are clinically relevant, encourage simplification of and compliance with AR management guidelines, ensure open and effective communication between all stakeholders and facilitate tailoring of AR medication to patients’ needs.

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P40
Deposition characteristics of a new allergic rhinitis nasal spray (MP29-02*) in an anatomical model of the human nasal cavity
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Background: Intranasal sprays must be delivered to the nasal cavity in sufficient volume, appropriate viscosity and droplet size and with a technique that allows optimal retention, maximizes absorption from the mucosa, and the potential for maximum therapeutic effect. The aim of this study was to evaluate nasal drug run-off after administration of MP29-02* (a novel intranasal formulation ofazelastine hydrochloride (AZE) and fluticasone propionate (FP) in an advanced delivery system) with sequential administration of marketed AZE and FP nasal sprays in vitro.

Methods: A normal adult human nasal cavity in vitro model was used [1,2]. A single spray of MP29-02* (0.137 mL [137µg AZE/50µg FP]) or single sequential sprays of AZE (0.137 mL [137µg AZE/0.50µg FP]) were applied during spray delivery to simulate inhalation.

Results: Three replicates of MP29-02* showed no dripping or back flow from the nasal cavity (i.e. anterior spray area or anterior drip = 0.00 cm2). In all replicates MP29-02* was observed to coat all turbinates up to the nasopharynx, but not the nasopharynx structure itself. However, three replicates of sequential sprays of AZE followed 1 min later by either branded or generic FP showed significant anterior nasal drip (i.e. run-off) from the nostril and also toward the back of the nasal cavity (i.e. posteriorly, which would be swallowed in vivo); AZE & branded FP: anterior spray area = 1.67 – 3.16 cm2; AZE & generic FP: anterior spray area: 0.68 – 1.83 cm2.

Conclusion: MP29-02* is a new AR treatment, comprising AZE and FP in a single spray in an improved formulation and device (vs marketed FP). In this model, the delivery of MP29-02* showed improved retention in the targeted areas compared to sequential administration of marketed intranasal monoproduts. These could not be administered together without run off (posteriorly and anteriorly) which could diminish efficacy.

References
Chronic rhinosinusitis with nasal polyps is hard to treat. The 2010, 161(4) such rhinitis with an association A novel P42 complain of bothersome symptoms Clinical and Translational Allergy aize, whereas methylprednisolone 126(3) 2012, Macchi: JACI vasomotor rhinitis, they are studied 129(5) after 4 weeks. Mepolizumab, doxycycline and methylprednisolone each treatment symptom scores worsen progressively and return to baseline compared to baseline, but not placebo. Methylprednisolone has initially R Ralph Mösges A new AR therapy (MP29-02*): all of ARIA in one puff the eosinophilic cascade. Beneficial effect of omalizumab seems to be mediated through a direct eosinophilic markers. Omalizumab did not reduce markers of eosinophilic inflammation in nasal secretions and assessment of symptom score and measurement of markers of inflammation in nasal secretions and serum at baseline, week 4 and week 8. All treatments were completed at week 4, except for 2 patients who received a fourth subcutaneous dose of omalizumab at week 6. Results: All treatment options significantly reduced nasal polyp score as compared to baseline, but not placebo. Methylprednisolone has initially the most dramatic effect on symptom scores, but after cessation of treatment symptom scores worsen progressively and return to baseline after 4 weeks. Mepolizumab, doxycycline and methylprednisolone each had a specific effect on local and systemic inflammatory markers. Omalizumab did not alter eosinophilia or markers of inflammation. Conclusions: Omalizumab, mepolizumab and oral doxycycline cause a long-term reduction in nasal polyp size, whereas methylprednisolone initially causes the strongest reduction in polyp size but recurrence occurs earlier. Total symptom scores parallel this trend. Mepolizumab and doxycycline work on eosinophilic and neutrophilic inflammation in nasal polyps, whereas the effect of methylprednisolone is apparent on eosinophilic markers. Omalizumab did not reduce markers of eosinophilic inflammation, nor neutrophilic inflammation in nasal secretions. The beneficial effect of omalizumab seems to be mediated through a direct effect on IgE or their receptor, rather than through an effect on markers of the eosinophilic cascade.

**P42**

A new AR therapy (MP29-02*): all of ARIA in one puff

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Allergic rhinitis (AR) is increasing in prevalence and becoming more difficult to treat. There is a subset of patients who are refractory to ARIA-defined rhinitis management approaches [1]. Even though new treatments have been made available for symptomatic relief, no new class of medication was forthcoming, until recently. This situation has now changed. MP29-02* is a novel intranasal formulation of azelastine hydrochloride (AZE) and fluticasone propionate (FP) in an advanced delivery system. It benefits from antihistamine, mast-cell stabilizing, anti-leukotriene and anti-inflammatory properties, made up in a unique formulation and delivered using an improved device (vs marketed intranasal steroid sprays (INS)). MP29-02*’s novel formulation and spray characteristics (e.g. finer droplet size, consistent spray release, wider spray angle) were developed to improve drug deposition on the nasal mucosa and ensure optimal retention. The impact has been observed both pharmacokinetically, [2] and clinically [3,4]. MP29-02* was created to be more effective than any existing symptomatic treatment for AR, have a rapid onset of action and a sustained effect. Delivered as a single spray from one device, the aim was to improve compliance, maximize convenience for patients and simplify dosing. This product provides more effective relief than currently considered gold standard treatment, INS. A recent publication by Meltzer et al, 4 re-assessed the efficacy of MP29-02* versus AZE and FP in an innovative and clinically relevant way by responder analyses. The authors determined different response cut-offs from 30 to 90% reflective total nasal symptom score (rTNSS) reduction from baseline. More MP29-02* patients achieved each response (vs FP or AZE), and days earlier. A response ceiling of ≥60% was identified above which INS failed to differentiate from placebo. This may explain why moderate/severe AR patients still complain of bothersome symptoms despite ARIA-guided treatment. Patients who remain symptomatic on monotherapy should experience a significant reduction in their symptoms with MP29-02*, exceeding that which they have experienced in the past, and many days faster than an INS. MP29-02* comprises all the pharmacological principles foreseen in the ARIA treatment algorithm.

**References**


**P43**

**Cellular rhinitis**

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Cellular rhinitis represent a form of vasomotor rhinitis, they are studied by means of the nasal cytology which allows through the taking of a minimum amount of mucus in the nasal mucosa of studying with an optical microscope such cells. The cells are stained with May Griwald Giemsa methods, such methods allows to highlight the major cellular components at the level of the surface layer of the nasal mucosa. The forms of rhinitis cell are represented by non-allergic eosinophilic rhinitis (NARES), nonallergic rhinitis by mast cell eosinophilic (NAREMSA), neutrophilic from non-allergic rhinitis (NARNE), nonallergic rhinitis by mast cell (Narma).

An epidemiological study in Italy, done by members dell’AICNA, Italian Academy of Nasal Citology) have highlighted these results on a population of 3872 people seen during a ENT visit: NARES 2.69%, 1.47% NARNE, 1.47% Narma, 16.50% allergic, 1.26% of narne, 2.38 overlapping, 70.53% normal, 1.47% yeast, 2.24 % bacterial.

Therefore represent a significant percentage of the vasomotor rhinitis. The therapy today is not defined so many type of therapy are used by the clinician so the academy try to establish a rule to treat this rhinitis so actually are in study the treatment of such rhinitis with an association between a topical steroid, fluticasone propionate with a topical antihistamine azelastine hydrochloride. The primary results are satisfactory in the treatment of NARES.