Oral Abstract Session 9

From Principles to Practice: Exploring Mechanisms of Asthma

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OAS-89

Pragmatic Randomized Controlled Trial for Stepping Down of Asthma Controller Treatment in Patients Controlled with Low Dose Inhaled Corticosteroid and Long-Acting Beta2 Agonist

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Background: Current asthma guidelines recommend stepping down of controller treatment when the asthma is well-controlled for certain period of time. However, in well-controlled patients on low dose inhaled corticosteroid (ICS) with long-acting beta2 agonist (LABA), the best stepping down strategy is still obscure.
Methods: This study was a randomized, open-label, 3 arm parallel pragmatic trial comparing two kinds of step down approaches to maintaining treatment. Adult asthmatics aged 18 years or older who had been stable with low dose ICS/LABA for at least 3 months were enrolled in 20 hospitals participating in COREA asthma research network. Subjects were randomly allocated into 3 groups (maintaining low dose ICS/LABA (G1), discontinuing LABA (G2), and reducing ICS/LABA to once daily (G3)) and followed-up during 6 months. Primary endpoint was the ACT change between randomization and 6 months follow-up points. Key secondary endpoints were the slope of ACT change and treatment failure rate.
Results: A total of 231 patients were enrolled and 225 subjects were randomly allocated to three groups. The ACT change was analyzed with PP set population and non-inferiority was not demonstrated in both stepping-down groups compared to maintaining group (95% confidence interval (CI) of the difference; G2 vs. G1=−1.40~0.55, G3 vs G1=−1.19~0.77) as 95% CI included the non-inferiority margin of −1. Higher rates of treatment failure was observed in stepping down groups than maintaining group (G1: 0%, G2: 9.46%, G3: 9.09%, p=0.027). There was no significant difference between two stepping down approaches in terms of ACT change and treatment failure.
Conclusion: Non-inferiority was not demonstrated in both stepping-down groups compared to maintaining group. About 10% of patient experienced treatment failure following 6months after step-down. Further studies are needed to define high risk patients for clinical deterioration when stepping down.

Key Words: Asthma, Step down, Treatment

OAS-90

Comparisons of Clinical Features among the Different Phenotypes of Airway Inflammation in Adult Asthmatics

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Backgrounds: Asthma phenotypes are often defined by relative cell counts of airway granulocytes. Induced sputum test has allowed to subdivide asthma patients into inflammatory phenotypes according to the degree of eosinophils and neutrophils. The aim was to investigate the clinical characteristics of patients with asthma according to the inflammatory phenotypes.
Methods: Data on 137 patients with asthma reported in a single tertiary allergy center in Korea during October 2016 to January 2019 were obtained. Patients were categorized in the four phenotypes according to cell counts in induced sputum. The data included blood eosinophils, total IgE, eosinophil cationic protein, spirometric measurements, fractional exhaled nitric oxide (FeNO), atopy based on skin prick test, the presence of sinusitis, methacholine PC20, the kind of asthma controllers, and the frequency of exacerbation.
Results: The frequency of each phenotype as follows: eosinophilic (27%), neutrophilic (34%), mixed (12%), and pauci-granulocytic types (27%). Blood eosinophils were higher in eosinophilic type compared to neutrophilic type ($p<0.05$). FeNO was higher in eosinophilic type compared to neutrophilic and pauci-granulocytic types ($p<0.001$ and $p<0.001$, respectively). PC20 values expressed as median (IQR) were 0.57 (0.01-9.24), 0.86 (0.08-13.61), 2.94 (0.05-12.8), and 3.31 (0.31-12.81) for eosinophilic, pauci-granulocytic, neutrophilic and mixed types, respectively, indicating that patients with neutrophilic and mixed types had milder airway hyperresponsiveness (AHR) ($p<0.05$). Interestingly, 34% of patients with neutrophilic type had severe exacerbation that requires visiting the emergency department.
Conclusions: Neutrophilic asthma may show more frequent severe exacerbations despite regular asthma medications, although the degree of AHR is milder, possibly due to less therapeutic response to inhaled corticosteroid.

Key Words: Exacerbations, Induced sputum test, Neutrophilic asthma

OAS-91

Clinical Features and Outcomes of Newly Diagnosed Asthma by Blood Eosinophil Count

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Background: Eosinophils are a major inflammatory cell involved in the pathophysiology of asthma. Sputum eosinophil is associated with disease severity, treatment outcome, and prognosis in asthma patients. However, it has not been elucidated whether blood eosinophil is related to that of asthma.
Objective: We investigated the clinical features, lung function and treatment response according to blood eosinophil level in newly diagnosed asthma patients.
Methods: This retrospective study included a total of 174 newly diagnosed asthma patients with naive inhaled corticosteroid (ICS) who visited the allergy clinic at Dong-A University Hospital from January 2014 to December 2018. We compared the clinical features of bronchial asthma, lung function and treatment response for 1 year according to initial blood eosinophil count: <300cells/uL (group I, n=74); 300-700cells/uL (group II, n=65); ≥700cells/uL (group III, n=35).
Results: There were no significant differences in sex and age among three groups. Most subjects were treated with ICS (89.2 vs 95.4 vs 97.1 %, P=0.204). Baseline FEV_1 in group I was lower than that in group II and III (1.81±0.95 vs 2.18±0.88 vs 2.12±0.98 L, P=0.057). The greatest increases in FEV_1 after 1 year was observed in group III followed by group II and I (36.92±371.05 vs 195.25 ±569.21 vs 353.82±594.84 mL, P=0.011). There were no significant differences in the proportion of patients with tapering or stop of ICS and the number of exacerbation during the first year (45.5 vs 61.3 vs 55.9 %, P=0.191 for change of ICS; 0.58±0.84 vs 0.42±0.64 vs 0.37±0.84, P=0.302 for exacerbation).
Conclusion: Newly diagnosed asthma patients with elevated blood eosinophil count showed better improvement in lung function for 1 year treatment. However, there were no significant differences in change of ICS requirements and the number of exacerbation according to blood eosinophil count in our study population.

Key Words: Asthma, Blood eosinophil

OAS-92

Early Detection of Lung Ventilation Disorder by Methacholine Challenge Test

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Purpose: According to the scientists, the prevalence of asthma worldwide is about 4-10%, and it shows the upward trend every year. In Ulaanbaatar, the prevalence of asthma was 2.1% and 5% among adult population in 2000 and 2010, respectively. The winter season is a coldest and highest air polluted period of time by CO, SO2, NO2, and PM20 in Ulaanbaatar and it is become risk factor of airway hyper-responsiveness. Therefore, we aimed to diagnose asthma by using methacholine challenge test and detect airway hyper-responsiveness.
Methods: We obtained 64 subjects with asthma-like symptoms and normal lung function by spirometer. The lung ventilation function was defined by parameters including FEV1, FVC, PEF, FVC/FEV1 using spirometer test (Spirostar USB, Spiro 2000 2.1 software Medikro OY). Methacholine challenge test were done by 5 steps nebulization with 2.5 and 25 mg/ml methacholine. We have measured if pre-test and post-test difference reduced by more than 20%, as a result of the test positive.
Results: We were interviewed 16-60 (average age 35±12) aged 64 subjects with asthma symptoms and normal lung function by spirometer. 89.6% (95% CI: 92.4-86.9) out of subjects had positive results on MCT in winter season with air polluted by CO, SO2 and PM20. 18%, 36% and 46% out of patients with positive results on methacholine challenge test were severe, moderate and mild changes respectively. 68.9% out of subjects with airway hyper-responsiveness were sensitized to aeroallergens. 73.4% out of them strongly sensitized to mugwort (mean size of wheals 17±3.1 мм).
Conclusion: The winter season is a coldest and highest air polluted period of time by CO, SO2 and PM20 in Ulaanbaatar and it is become strongly risk factors of airway hyper-responsiveness.

OAS-93

Analysis of High-Resolution CT Features According to the Lung Function Trajectory Types in Never-Smoking Adults with Asthma

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We has reported the article of lung function trajectory types in never-smoking adults with asthma (Allergy Asthma Immunol Res. 2018 Nov;10(6):614-627). Trajectory clustering analysis of FEV1 identified 5 distinct types. Trajectories 4 and 5 were associated with severe asthma. In trajectory 4 and 5, two phenotypes of severe asthma have been documented anatomical changes in the airway as compared to mild asthma. However, there has been little analysis of the airway structural changes between trajectory 4 and 5.
The chest CT visual assessments were scored about eight HRCT findings by two categories to evaluate reversible and irreversible changes; Macroscopic changes-evaluating irreversible changes including emphysema, bronchiectasis, anthracofibrosis, bronchial wall thickening, fibrotic band and microscopic changes (small airways disease) - evaluating reversible changes including mosaic attenuation in inspiration, air-trapping in expiration, centrilobular nodules. Each lung was divided into three lung parts and the CT features were scored either present (score of 1) or absent (score of 0) in each lung zone and the range of score were 0-6 for each patient of trajectory 1 (n=13), trajectory 2 (n=23), trajectory 3 (n=23), trajectory 4 (n=22) and trajectory 5 (n=21).
Trajectory 4 and 5 were significantly higher in emphysema, bronchial wall thickening, fibrotic band and mosaic attenuation in inspiration than trajectory 1,2 and 3 ($P<0.05$). Trajectory 5 was significantly increased emphysema, bronchiectasis and fibrotic band compared to trajectory 4 ($p<0.05$).
Drug-resistant airway remodeling in trajectory 5 might be due to macroscopic irreversible changes of emphysema, bronchiectasis and fibrotic band.
The clinical informations of subjects were provided by a BioBank at Soonchunhyang University Hospital, and funded 2016-ER7402-00.

Key Words: HRCT, Trajectory 4 and 5, Macroscopic irreversible changes

OAS-94

Mitochondria-associated NLRP3 Inflammasome Contributes to the Neutrophilic Lung Inflammation

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Neutrophilic inflammation is considered as one of the essential portions in the pathogenesis of severe allergic inflammation. Recent studies have demonstrated that NLRP3 inflammasome activation plays a critical role in various pulmonary inflammatory disorders. Besides, mitochondrial reactive oxygen species (ROS) induce the assembly of the NLRP3 inflammasome. In this study, we aimed to evaluate the localization of NLRP3 in mitochondria of various inflammatory cells under LPS-induced neutrophilic pulmonary inflammation and pharmacologic effects of MCC950, a specific NLRP3 inhibitor on LPS-induced neutrophilic pulmonary inflammation using animal models and human samples. LPS-instilled mice showed typical features of neutrophil-dominant acute lung injury; pulmonary neutrophilia, vascular leakage, nuclear translocation of nuclear factor-κB (NF-κB), increased expression of Toll-like receptor 4 (TLR4), and mitochondrial ROS generation. Interestingly, the NLRP3 inflammasome activation indicators, NLRP3, caspase-1, IL-1β, and IL-18 were dramatically increased in lung tissues, particularly in the mitochondrial fraction. Moreover, we also found that NLRP3 inflammasome effecter cytokines; mature IL-1β and IL-18 as well as mitochondria fractions were increased in the plasma from patients with neutrophilic acute lung injury. When MCC950 or NecroX was administered to LPS-instilled mice, mice showed the dramatic improvement of all inflammatory features including NLRP3 inflammasome activation, particularly in the mitochondrial fractions. These findings suggest that NLRP3 inflammasome assembly, especially mitochondrial-associated NLRP3 plays critical roles in the pathogenesis of LPS-induced pulmonary inflammation and that plasma NLRP3-related proteins or mitochondrial volume can be a biomarker predicting the severity and therapeutic responses of the inflammasome inhibitors in neutrophilic severe pulmonary inflammations.

Key Words: NLRP3 inflammsome, Mitochondria, Neutrophilic inflammation

OAS-95

Epithelial Osteopontin: A Key Mediator of Late-Onset Asthma

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Background: Patients with late-onset asthma (LOA) were older and present poor lung function/clinical outcome. Osteopontin (OPN), a multifunctional protein expressed in epithelial cells, is associated with airway inflammation and remodeling.
Objective: We investigated OPN in patients with LOA vs. early-onset asthma (EOA) in an asthmatic cohort. The effect of respiratory virus and aging on OPN production was studied using an in vitro and an in vivo system.
Materials & Methods: We enrolled 134 adult asthmatics (45 LOA, 89 EOA patients) and 121 healthy controls (HCs) from Ajou Medical Center, Suwon, South Korea. Human airway epithelial cells (HAECs) were stimulated with polyinosinic-polycytidylic acid [Poly(I:C)] for 24 h. ELISA was used to measure the levels of OPN, IL-8, TGF-β1, IL-33 and chitinase 3-like-1 (YKL-40) in sera and culture supernatants. Mice at 6 weeks and 12 weeks old were used as controls (C-6wk, C-12wk, respectively) and to induce allergic asthma by ovalbumin sensitization (OVA-6wk [EOA], OVA-12 wk [LOA]), with or without Poly(I:C).
Results: Serum OPN level was significantly higher in asthmatic patients vs. HCs, in LOA vs. EOA ($P<0.05$ for all) and potentially discriminates LOA from HCs (AUC=0.853, 91.4% sensitivity, 52.7% specificity, $P<0.001$). High OPN responders had higher level of TGF-β1/YKL-40 levels with positive correlations between serum OPN and TGF-β1,YKL-40,IL-8 and age ($P<0.05$ for all). In an in vitro setting, Poly(I:C) induced release of OPN/IL-8/TGF-β1/YKL-40 from HAECs ($P<0.05$ for all). In an in vivo setting, OVA-12 wk showed significantly lower airway hyperresponsiveness with higher levels of OPN/TGF-β1/YKL-40 in bronchoalveolar lavage fluid (BALF) than OVA-6wk/C-6wk/C-12wk. Administration of Poly(I:C) induced the significant increase of OPN/ IL-33/ TGF-β1 in BALF.
Conclusions: Aging/ viral infections induce OPN production from HAECs, contributing to developing the LOA phenotype via modulating IL-8/TGF-β1/YKL-40 production

Key Words: Aging, Late-onset asthma, Osteopontin, Virus

OAS-96

Association between Lead Exposure and Increased Risk of Bronchial Asthma in Korean Adolescents

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Purpose: Several studies have reported an association between lead exposure and increased risk of allergic sensitization and asthma. According to CDC guidelines, An elevated blood lead level (BLL) is defined as a BLL≥5μg/dL. But No safe BLL has been identified and it is not known whether BLL<5μg/dl affects risk of asthma.
Methods: We examined asthma prevalence and BLL using data from the 2010-2013 Korea National Health and Nutrition Examination Survey (KNHANES), which was a cross-sectional survey of 1478 adolescence (aged 10-19 years) throughout the country. The adjusted odds ratio (aOR) (with 95% CIs) for the prevalence of asthma in adolescence with elevated BLLs were calculated by Complex samples multivariate logistic regression analysis.
The presence of asthma was based on self-reported, physician-diagnosed asthma in the Health Interview Surveys.
Results: The mean of total BLLs was 1.33μg/dL. Overall, 5.1% (n=71) of the subjects were physician diagnosed asthma. In the model controlling for population characteristics, the aOR for asthma per 1μg/dL increase in BLL was 1.94, 95% CI [1.06, 3.57] and stronger associations were observed among boys (aOR 2.31, 95% CI [1.18, 4.51]). The group of BLL≥2μg/dL was associated with an aOR of 2.84 (95% CI [1.06, 7.63]) for asthma, after adjusting for potential confounding factors in boys.
Conclusion: Our results suggest an association between BLLs and asthma in Korean adolescent boys, although confirmation is warranted in prospective studies.

Key Words: Lead, Asthma, Allergic

OAS-97

Biodegradable Transdermal Microneedle Immunotherapy Can Ameliorate Airway Inflammation in Murine Asthma Model

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Background: House dust mite (HDM) is a well-known cause of allergic asthma. Allergen specific immunotherapy (AIT) can modify the natural course of the disease. Conventional routes of HDM AIT used in the clinics are subcutaneous or sublingual. Limitation of subcutaneous AIT is risk of anaphylaxis, and sublingual AIT is low compliance and oro-pharyngeal discomfort. To overcome the weak points of conventional AIT, we developed a HDM loaded biodegradable transdermal microneedle immunotherapy (MNIT). We aim to demonstrate the efficacy of MNIT in murine asthma model triggered by HDM.
Method: To make HDM asthma mouse model, 5-week-old BALB/c female mice were sensitized and challenged by intranasal administration of HDM. The mice were divided into 5 groups: sham, asthma, low (10 μg) and high dose (100 μg) subcutaneous AIT, and MNIT (10 μg). To make HDM loaded MNIT patches, droplet-born air blowing method was used. Airway hyperresponsiveness, allergic inflammation markers were analyzed by broncho alveolar lavage fluid, immunohistochemistry, serum immunoglobulin (Ig) analysis, and lung cytokine assays.
Results: Airway hyperresponsiveness was ameliorated by MNIT. Eosinophilic inflammation in broncho alveolar lavage was improved without local or systemic adverse reactions. Reduction of Th2 (IL-4, IL-5, and IL-13) cytokines, and HDM specific IgE, induction of Treg (IL-10, TGF-β), Th1 (IFN-γ) cytokines was observed. Eosinophilic infiltration, goblet cell hyperplasia, and subepithelial fibrosis were also alleviated by MNIT. These changes were more significant in the MNIT group than in subcutaneous AIT group.
Conclusion: HDM loaded biodegradable transdermal MNIT is a novel treatment option to treat asthma.

Key Words: Asthma, Immunotherapy

OAS-98

Viable Aspergillus Fumigatus (Af) Conidium Can Induces Allergic Lung Inflammation Via Phosphoinositide 3-kinase (PI3K)-δ Signaling

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Delta (δ) isoform of phosphoinositide 3-kinases (PI3Ks) may be one of important therapeutic targets for treating inflammatory diseases. However, there are also concerns on PI3K-δ blockade due to its potential to disturb protective immune responses. We evaluated whether PI3K-δ inhibition can affect on the progression of fungus-associated inflammation/infection in an experimental fungal allergic lung inflammation established through respiratory Aspergillus fumigatus (Af) conidium exposure. Respiratory exposure of Af led to the increases in the numbers of total cells, neutrophils, lymphocytes, and particularly eosinophils, in bronchoalveolar lavage (BAL) fluids. Levels of TH2 cytokines in lung tissues of Af-exposed mice were increased. IC87114, a potent inhibitor of PI3K-δ, significantly lowered the Af-induced increases of BAL cells, particularly eosinophils, and IL-4, IL-5, and IL-13 in the lung, while treatment with itraconazole failed to ameliorate. Concurrent treatment of IC87114 with itraconazole led to a tendency toward a better improvement of Af-induced allergic lung inflammation than IC87114 alone, although it was not statistically significant. We could not observe any significant increase in fungal colonization/infection associated with IC87114 in the lung and the numbers of neutrophils were not significantly changed in BAL fluids from Af-exposed mice. These data suggest that PI3K-δ blockade is effective for controlling Af-induced allergic lung inflammation without significant progression of inflammation and the infection in the current experimental system.

Key Words: Fungal allergy, PI3K-δ blockade, Infection

OAS-99

Chronic Anti-Asthmatic Effects of Mesenchymal Stem Cells on a Murine Model with Overexpressed Lung-Specific Interleukin-13

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Background: Stem cells have been researched to prove their therapeutic potentials on chronic inflammatory diseases. Mesenchymal stem cells (MSCs) are ones of the most frequently used stem cells and have been reported to have an anti-asthmatic effect in murine model.
Objective: The study aimed to evaluate therapeutic effects of umbilical cord (UC)-derived MSCs primed with liproxstatin-1 on chronic asthmatic inflammation induced by interleukin (IL)-13.
Method: Seven- to eight-week-old transgenic (TG) mice, which are constitutively overexpressing lung-specific IL-13, were used to represent chronic asthma. Human UC-MSCs (hUC-MSCs) primed with liproxstatin-1 were intratracheally administered four days prior to sacrifice. Differential counts of bronchoalveolar lavage (BAL) fluids, histological analysis, and flow cytometry were performed to compare the phenotypes among groups.
Result: IL-13 TG mice showed severe airway inflammation, characterized by eosinophilic infiltration, mucus metaplasia, and lung fibrosis. Administration of hUC-MSCs to IL-13 TG resulted in significant reduction in total number of inflammatory cells, eosinophils, neutrophils, and lymphocytes in BAL fluids. Semi-quantitative scoring based on histological analysis revealed decreased inflammatory cell recruitments in the lungs of mice treated with hUC-MSC. Additionally, fibrosis and mucus production reductions were observed in trichrome and PAS staining. Flow cytometry indicated that suppression of innate lymphoid cells (ILCs) as well as CD4+ T cells by IL-13 overexpression and these suppressions were reversed by administration of liproxstatin-1-primed hUC-MSCs.
Conclusion: Liproxstatin-1-primed hUC-MSCs effectively reduced chronic asthmatic inflammations induced by IL-13 overexpression, such as eosinophil infiltration in the airway, mucus metaplasia, and fibrosis. The results suggest that the administered MSCs play an interfering role in negative feedback circuit of IL-13 on T lymphocytes and ILCs.

Key Words: Asthma, Mesenchymal stem cells, Cell therapy, Interleukin-13