Oral presentation 3

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· **Chairs:** Jung-Won Park (Yonsei Univ.), Dong-Young Kim (Seoul Nat'l Univ.)

OP-23

HLA-DR*15:02 allele increases the risk of low osmolar contrast media induced anaphylaxis

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Background: As the use of iodinated contrast media (ICM) increases, the adverse reactions are also increasing. Among them, anaphylaxis is getting more attention according to its fatal consequences. However, there is no effective method for predicting anaphylaxis in patients other than a previous history. To develop the strategy of risk prediction based on genetic susceptibility, we analyzed the association between severe anaphylaxis to ICM and human leukocyte antigen (HLA) genotypes.
Methods: We searched patients who ever experienced anaphylaxis with administration of low osmolar ICM in the Korean registry of ICM adverse reaction. After obtaining consent to participate, blood samples were collected from for genotyping of HLA A, B, C, DR. Their genotypes were compared with those of Korean general population.
Results: A total of 23 patients suffering anaphylaxis to ICM were recruited. Their genotypes of HLA-A, B, C were not different from those of Korean general population. However, while DRB1*15:02 allele was positive in 6.6% of the general population in Korea, 30.4% in the anaphylaxis group had DRB1*15:02 allele. The risk for the development of ICM-induced anaphylaxis was significantly increased with this allele (OR 6.2 [95% CI 2.38-16.14], p=0.00002).
Conclusion: A significant association of ICM-induced anaphylaxis with the HLA-DRB1*15:02 allele was observed in a Korean population. The results suggest that HLA-DRB1*15:02 allele may contribute to the development of ICM-induced anaphylaxis.

Key Words: Contrast media, Anaphylaxis, Genes, Risk Factors, HLA

OP-24

Nationwide registry study of iodinated contrast media hypersensitivity

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Background: Iodide contrast media (ICM) hypersensitivity reactions are rare but could be life-threatening. More than 4 million iodine contrast media are used annually in Korea and expected to increase further. However, prospective studies on the epidemiology and risk factors of ICM hypersensitivity reactions are insufficient.
Methods: The status of ICM use and the occurrence of hypersensitivity reactions were investigated in seven hospitals nationwide. The definition of hypersensitivity and severity, consent form, patient information survey and treatment protocol were standardized in the participating hospitals. The data were collected prospectively for 8 months through registry system of Korea national institute of health. For the follow-up of recurrence, both new and past ICM hypersensitivity patients were enrolled in the cohort. To determine the effect of risk factors, a 1: 1 control group was set up in accordance with age, sex, and product of ICM.
Results: During the 8 months of 2017/3/1 to 2017/10/31, the total number of ICM used in 7 institutions was 194,493, a total of 1,401 (0.72%) hypersensitivity reactions were occurred. A total of 22 ICM products and 7 components were used during the study period. The incidence of hypersensitivity varied from 0.37 (Iopromide) to 0.99 (Iodixanol) depending on the ICM components. The severity was mild 83.1% moderate, 15.9% and severe 1.1%. Overall, 70% of patients recovered without any special measures and only 4% required intensive treatment such as emergency room transportation. A history of hypersensitivity reaction, family history, drug allergy, allergic disease, and asthma were identified as a significant risk factor for ICM hypersensitivity reaction.
Conclusion: The incidence of hypersensitivity reaction of ICM was 0.72%, and it varies by product and component of ICM. The influence of genetic predisposition may be suspected because family history is a risk factor for ICM hypersensitivity.

Key Words: Contrast media, Hypersensitivity, Registries, Risk Factors

OP-25

Differences in Adverse Reactions among Iodinated Contrast Media: analysis from KAERS database

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Background: There are few studies about incidence of acute drug reactions(ADRs) considering total usage of contrast media. Thus, we investigated occurrence rate and types of ADRs according to total usage of most commonly used seven contrast media (iobitridol, iodixanol, iohexol, iomeprol, iopamidol, iopromid and ioversol).
Methods: We reviewed 76682 ADRs of Korea Adverse Event Reporting System (KAERS) database reported to be caused by contrast media between January 2014 to December 2016. Among them, 238 cases considered less relevant to contrast media by causal evaluation were excluded. Thus, 74242 cases were finally included in this study. Further analyses will be performed considering usage of contrast media reported from individual medical institution for the precise estimation.
Result: Based only on the reported cases regardless of usage, the contrast media with the most common ADRs was iohexol (9041, 20.7%) and followed by iopamidol (8853, 20.2%), iopromide (7734, 17.7%), iomeprol (7334, 16.8%), iobitridol (5128, 11.7%), ioversol (3725, 8.5%) and iodixanol (1808, 4.1%). In all 2409 serious adverse events, iomeprol (479, 19.8%) is the most, followed by iohexol (454, 18.8%), iopamidol (444, 18.4%), iopromide (418, 17.3%), iodixanol (225, 9.3%), iobitridol (208, 8.6%) and ioversol (181, 7.5%). In classification of ADRs according to systemic organ class, skin and appendages disorders (47065, 63.3%) were the most common, followed by gastro-intestinal system disorders(10147, 13.6%). In addition, immediate hypersensitivity (44467, 88.56%) showed more frequent than delayed (5725, 11.4%).
Conclusion: The incidence of adverse reactions was different according to respective contrast media. These differences of seven seven contrast media may be considered when monitoring patients during and after its use to promote patient safety.

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Key Words: Contrast Media, Adverse Drug Reaction

OP-26

Eperisone Related Adverse Drug Reactions Including Anaphylaxis: a Study on 242 Korean Patients

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Background: Eperisone is an oral muscle relaxant used in musculoskeletal disorders with muscle spasm. Eperisone is often prescribed with NSAIDs. In that reason, eperisone related adverse drug reaction (ADR) has been overlooked. The purpose of this study was to analyze the nationwide ADRs reported in Korea and suggest diagnostic approach of eperisone induced ADR including anaphylaxis.
Methods: We reviewed eperisone-related pharmacovigilance data reported in Korea from 2010 to 2015. ADRs with causal relationship were selected. Clinical manifestations, severity, outcomes, and re-exposure information were analyzed. For further investigation, 7 years of ADR data reported in a single center was also reviewed. Oral provocation test, skin prick test, basophil activation test were performed in this center.
Results: During the study period, 207 patients suffered adverse reactions to eperisone in Korea. Mean age was 55.4 years old and 67.1% of the patients were female. The most common ADRs were cutaneous manifestations including urticaria, rash, and angioedema (30.4%). Gastrointestinal symptoms were second common ADRs (25.1%). Out of these, 32 (15.5%) patients were reported to have serious ADR, 35 (16.9%) patients were re-exposed and symptoms were reproduced. There were 35 patients with anaphylaxis, representing 16.9% of the patients. In a single center study, 35 patients were selected to analysis. Among them, 12 patients were agreed and underwent oral provocation test. All the provoked patients showed positive reaction. There were 9 patients of eperisone induced anaphylaxis. Two anaphylactic patients were also underwent skin prick test and basophil activation test, and those were all negative.
Conclusions: Eperisone can cause diverse ADRs, including anaphylaxis. We reported 44 patients with eperisone induced anaphylaxis. Eperisone is thought to induce non-IgE mediated immediate hypersensitivity based on the small number of mechanism studies.

Key Words: eperisone, hypersensitivity, anaphylaxis

OP-27

Therapeutic effects of Mesenchymal stem cells in an animal model of Stevens-Johnson and Toxic Epidermal Necrolysis

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) are very rare but extremely severe drug adverse reactions which affect skin and mucous membranes. The pathologic mechanisms of SJS/TEN are not fully known. Especially, no one has been able to explain why these systemic cell-death mediators affect skin exclusively and result in widespread mucocutaneous erosions without dysfunction of other organs. Aims of this study are setting up the mouse model of SJS/TEN and verification of therapeutic effects of mesenchymal stem cells in this animal model. To set up an animal model, immunocompromised NOD/Shi-scid, IL-2R γ null (NOG) mice were used. PBMCs isolated from a SJS patient's blood (F/45y) were injected only one time into the tail vein, and then a causative drug was administered daily for 14 days from the start date of this experiment into the oral of NOG mouse. For examination of therapeutic effects, MSCs were once injected intravenously 14 days after PBMCs injection. Finally, these mice were sacrificed 28 days after the PBMCs injection. H&E staining showed morphological differences of the mouse eyeballs among the experiment groups. The eyeballs of no treatment mouse, PBMC-only injected mouse, and drug-only treated mouse had healthy conditions of cornea, limbus, nuclear layers, and eyelids, respectively. However, the eyeballs of PBMC&drug treated mouse had damaged the shape of eye lens, cornea, limbus, nuclear layers and eyelids. And, MSCs therapy mouse showed similar conditions with healthy groups by the therapeutic effects of MSCs. TUNEL staining had displayed several apoptotic death cells of nuclear layers and circumocular tissues in PBMC&drug treated mouse. But, any other mice rarely had apoptotic death cells in their eyeballs sites. These results show that a setting up the SJS/TEN animal models by using immunodeficiency mouse, patient's PBMCs, and a causative drug, and could be presented the possibility of MSCs as a therapeutic candidate in SJS/TEN.

Key Words: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, Drug Hypersensitivity, Mesenchymal Stem Cells

OP-28

Novel smartphone based interactive system to prevent food allergy in school

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Introduction: As most school provides lunch group meals for all students in Korea, students with food allergies are at risk of exposure to their own allergenic components contained in school meal. Although there have been increasing event related to food allergies, no active intervention to prevent food allergy existed in school itself. We aimed to develop a smartphone application to prevent adverse allergic events from school group meals.
Methods: Monthly table of school meal with allergen labeling can be viewed at the website of National Education Information System (NEIS). Students with food allergies downloaded the application at Google Play store or Apple's App stores, and selected their school and allergenic components among 18 food allergens prespecified by the Food and Drug Administration. Their smartphone application downloaded the data throughout parsing the web server of NEIS, and provided information for allergenic components in daily school food. The app automatically sent 'food allergy alert' to students, their parents, and/or even their homeroom teachers.
Results: From September 2017 to December 2017, 42 students with food allergies were enrolled from 5 elementary schools in Cheong-Ji. The students with food allergies and their parents used the application for 12 weeks and surveyed the satisfaction for 'Allergy Alert in School Food' Application. The survey responders answered that this application might be helpful to prevent allergic adverse events in school food (3.8 points out of 5 points).
Conclusion: We developed the smartphone-based novel interactive system to prevent food allergy accidents in school. Student with food allergy and their parents answered that this application could be helpful to prevent exposure to allergenic components in school meal.

Key Words: Food allergy, School, Smartphone

OP-29

Clinical and Laboratory Findings of Barley Allergy in Korean Children: single hospital based retrospective study

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Purpose: Barley is widely consumed as steamed barley, barley tea, breads, and cookies especially in Asia, but reports on barley allergy are limited to few case reports of hypersensitivity reactions to beer. The study aimed to identify clinical and laboratory findings of barley allergy in Korean children.
Methods: Forty-four subjects who underwent serum specific IgE to barley (barley-sIgE) assay, with a history of ingesting barley, were enrolled through a retrospective review of medical records from March 2008 to February 2018, at the Department of Pediatrics in Ajou University Hospital. Demographic profiles, clinical symptoms, and laboratory findings were evaluated.
Results: Twenty-two patients showed clinical barley allergy (Allergic group), and 22 were atopic controls without allergic reactions after ingestion of barley (Tolerant group). The median ages in Allergic group and Tolerant group were 1 year and 3 years, respectively. In Allergic group, cutaneous system (90.9%) was most commonly affected, followed by respiratory system (36.4%). Anaphylaxis was noticed in 31.8%. Symptom onset time was < 5 minutes in 18.2%, between 5-30 minutes in 36.4%, and between 30-60 minutes in 27.3%. The median level of barley-sIgE was 11.04 kUA/L (0.02-101 kUA/L) for the Allergic group, which was significantly higher ($p < 0.001$) than 0.30 kUA/L (0.01-24.40 kUA/L) for the Tolerant group with the optimal cutoff level of 1.24 kUA/L (sensitivity 77.3%, specificity 86.4%). The median levels of barley-sIgE in anaphylactic and non-anaphylactic allergic subjects were 21.00 kUA/L and 2.07 kUA/L, respectively, with the optimal cutoff level of 5.30 kUA/L ($p=0.04$, sensitivity 100%, specificity 66.7%).
Conclusion: About 32% of children with barley allergy experienced anaphylaxis. The optimal cut-off level of barley-sIgE to distinguish the Allergic and Tolerant groups was 1.24 kUA/L.

Key Words: Barley allergy, Anaphylaxis, Children

OP-30

Role of TLR9 Signaling on Activation of Nasal Polyp Derived Fibroblasts and its Association with Nasal Polypogenesis

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Background: Nasal polyposis is characterized by persistent inflammation and remodeling in sinonasal mucosa. Toll-like receptor 9 (TLR9) is a DNA receptor of the innate immune system that plays a pivotal role in fibrosis and inflammatory responses. The aim of this study is to explore the expression, activity and potential pathogenic role of TLR9 signaling in tissue remodeling in nasal polyp derived fibroblasts (NPDFs).
Materials and Methods: Fibrotic and inflammatory responses elicited by type A CpG oligonucleotide were examined in the NPDFs by a combination of real-time quantitative polymerase chain reaction, Western blot analysis, enzyme-linked immunosorbent assay and immunofluorescence staining. For these experiments, the NPDFs were stimulated with different TLR9 agonists (CpG A and B) and blocked with inhibitors (MyD88 inhibitor and chloroquine).
Results: TLR9 expression was significantly higher in NP tissues compared to control or CRS mucosa. In the NPDFs, TLR9 showed intracellular localization and expression of TLR9 was increased after treatment with CpG A. CpG A increased production of α-SMA, fibronectin and Matrix metalloproteinase (MMPs) (MMP1, MMP2, and MMP9) in the NPDFs, while MyD88 inhibitor and chloroquine, which are known to block the TLR9 signaling pathway, inhibited their production. CpG A also produced type I interferon (IFN-α and INF-β) which were inhibited by MyD88 inhibitor.
Conclusion: Our data indicates that CpG A-induced fibroblast activation and cytokine production were mediated via TLR9 stimulation in NPDFs. Disrupting this process with an inhibitor targeting TLR9 or its downstream signaling pathways could represent a novel approach to CRSwNP therapy.

Key Words: chronic rhinosinusitis; innate immunity and rhinosinusitis; epithelial cell

OP-31

B-cell activating factor as a biomarker for refractory chronic rhinosinusitis with nasal polyps

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Background: Effective treatment of chronic rhinosinusitis with nasal polyp (CRSwNP) requires careful endoscopic sinus surgery followed by an individualized treatment that often includes oral and topical steroids. Regardless of technical advances, including a modern treatment protocol, some cases of nasal polyps (NP) show recidivism. However, the exact pathophysiology of refractory CRSwNP remains unclear.
Objective: The objective of this study was to characterize the immunologic profiles of refractory CRSwNP according to NP subtypes and find a target molecule.
Methods: Control (N=7), primary NP group (pNP, N=70), and refractory NP group (rNP, N=86) were enrolled in this study. Patients who required revision surgery due to failed medical treatment after primary surgery were defined as rNP group. Twenty inflammatory markers were investigated in nasal tissues using multiplex cytokine assay and ImmunoCap. Immunologic profiles according to NP subtype were characterized and key cytokines in rNP were identified. A potential therapeutic molecule was tested using ovalbumin (OVA)- and staphylococcal enterotoxin B (SEB)-induced murine NP model.
Results: B cell activating factor (BAFF), neutrophils-associated mediators (MPO and IL-8), Th17 cytokines (IL-17A, IL-22, and IL-23) and Th1 cytokine (IFN-γ) were up-regulated in rNP than controls and pNP. Human neutrophil elastase positive cells were also enhanced in rNP compared with pNP. There were positive correlations between BAFF and Th17/Th1 cytokines in rNP, regardless of tissue eosinophilia. Asthmatics with rNP showed higher levels of total IgE, ECP, and CCL24 than non-asthmatics with rNP. However, MPO, IL-17A, IL-23, IFN-γ, and BAFF were up-regulated irrespective of asthma comorbidity. Anti-nuclear autoantibodies including anti-dsDNA IgG were at higher levels in NP than controls, especially in asthmatics with eosinophilic rNP. To confirm whether the role of BAFF on NP formation, an anti-BAFF antibody was administrated in an OVA/SEB-induced murine model of NP. BAFF strongly correlated to neutrophil -associated cytokines such as IL-17A, IL-23p19, IL-6, CXCL-1 and anti-dsDNA IgG Ab in the murine NP model. With BAFF blockade, infiltration of neutrophils, the expression levels of CXCL-1, IL-23p19, IL-6, anti-dsDNA IgG Ab and IL-5 were effectively decreased.
Conclusion: Our data suggest that BAFF may play an important role in neutrophilic inflammation of refractory CRSwNP and can be a potential therapeutic target for patients with refractory CRSwNP.
Key Words: chronic rhinosinusitis, nasal polyps, B cell activating factor

OP-32

The role of IL-17 in CRS wth Nasal Polyp

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Introduction: Recently, IL-17 is known to play an important role in inflammatory disease including CRS. It is known to be increased in CRS with nasal polyp (NP). In this study, we evaluated the expression of IL-17 in CRS tissues and identified the cellular source of IL-17 in CRS with NP.
Methods: The expression of IL-17 in human CRS tissues were evaluated using PCR and immunohistochemistry (n=20 each group). And the cellular sources of IL-17 were evaluated with double staining immunohistochemistry using confocal microscopy. IL-17A, CD68, CD163, ELA2 CD56, CD4 and CD11c antibodies were used to evaluate the cellular sources of IL-17. Eosinophilic and non-eosinophilc polyps were evaluated (n=5 each sample). In addition, IL-17 blocking antibody was used in mouse model of CRS.
Results: PCR and IHC showed that IL-17 expressions were increased in both eosinophilic and non- eosinophilic polyps, wih significantly higher expression in noneosinophilic nasal polyp. Confocal staining revealed that about 60% of CD68+ M1 macrophage, 30% of ELA2+neutrophil and 10% of CD4 T cell coexpressed IL-17 irrespective of eosinophilic and noneosinophilc polyp, showing that M1 macrophage and neutrophil were major sources of IL-17 in nasal polyp. NK cell, M2 macrophage and dendriti cells did not produce IL-17 in both eosinopholic and non-eosinophilic nasal polyp. In animal model study, IL-17 blocking antibody significantly reduced polyp counts and inflammatory cytokines in nasal tissues significantly, suggesting the important role of IL-17 in CRS with NP.
Conclusion: These data showed that iL-17 were highly expressed in nasal polyp and the major cellular sources are macrophage and neutrophil, and that IL-17 might be used as target therapy in CRS with NP.

Key Words: IL-17, Nasal polyp

OP-33

Vitamin D inhibits TGF-β1-induced myofibroblast differentiation and extracellular matrix production via Smad2/3 signaling pathway in nasal polyp-derived fibroblasts

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Purpose: Nasal polyps are associated with chronic inflammation of the mucous membranes in the nose and paranasal sinuses and involved in extracellular matrix (ECM) accumulation. Vitamin D has a wide range of antifibrotic properties, including anti-inflammation, anti-proliferation, anti-apoptosis, and anti-epithelial-mesenchymal transition properties. This study aimed to determine whether vitamin D affects the myofibroblast differentiation and extracellular matrix synthesis and to investigate the mechanism of action of vitamin D in nasal polyp-derived fibroblasts (NPDFs).
Methods: We examined the effect of vitamin D on myofibroblast differentiation and ECM production in TGF-β1-induced NPDFs and elucidated the mechanisms underlying the inhibitory effect. 1,25(OH)2D3 significantly reduced the expression levels of α-SMA, a myofibroblast marker, and fibronectin, a representative ECM component, in a dose-dependent manner in TGF-β1-NPDFs.
Results: 1,25(OH)2D3 suppressed activated Smad2/3 in time-course. Up-regulation of α-SMA, fibronectin and phosphorylation of Smad2/3 by TGF-β1 were unaffected by 1,25(OH)2D3 in NPDFs after vitamin D receptor specific siRNA transfection. We confirmed inactivation of Smad2/3 and reduced level of α-SMA and fibronectin expression by the Smad2/3 specific inhibitor, SIS3. Furthermore, acetylation of histone H3 was compromised by 1,25(OH)2D3, leading to inhibition of collagen 1A1, collagen 1A2 and α-SMA gene expression. Treatment with 1,25(OH)2D3 also significantly suppressed TGF-β1-enhanced contractility and motility in a contraction assay and Transwell migration assay. Finally, 1,25(OH)2D3 had a similar effect in ex vivo organ cultures of nasal polyps.
Conclusions: Our results suggest that 1,25(OH)2D3 might be an effective therapy for treating nasal polyps by reducing myofibroblast differentiation and ECM production mediated by Smad2/3-dependent TGF-β1 signaling pathways in NPDFs

Key Words: Vitamin D, TGF-β1, myofibroblast differentiation