INTRODUCTION

Allergic diseases, including asthma, allergic rhinitis, atopic dermatitis, and food and drug allergies cause considerable morbidity and mortality worldwide. As lifestyles and environments have changed to become more urbanized and industrialized, the incidence and prevalence of allergic diseases has increased, and the study of allergy has become one of the most important fields in medicine. Allergy remains an important and unsolved problem for clinicians and researchers; however, the progressive development of immunology, pharmacology, and molecular biology has broadened our understanding of the mechanisms underlying allergies and has provided us a way to treat patients suffering from allergic diseases.

Although allergicology was only recently introduced in Korea, Korean allergology has made great progress in keeping pace with global scientific advances in spite of a short history. Outstanding academic and scientific researches have been performed in a variety of allergy fields in Korea. Epidemiologic studies revealed increasing prevalence of asthma and allergic diseases and considerable morbidity and mortality in Korea. Novel inhalant allergens such as citrus red mite and two-spotted spider mite as causes of asthma and allergic rhinitis have been discovered and reported in Korea. Bidirectional translational researches have been performed and are underway to elucidate the pathogenesis of asthma and allergy, mechanisms of airway inflammation and remodeling, and new therapeutic modalities for asthma and allergic diseases. Experimental asthma models of different phenotypes according to exposed levels of lipopolysaccharide or double-stranded RNA suggested the crucial role of the innate immunity in the development of allergic airway inflammation and a new insight for asthma pathogenesis, in which both Th1 and Th2 inflammation are involved. In the field of genetic researches, numerous genetic associations with asthma and asthma-related phenotypes, such as atopy, IgE production, and airway hyperresponsiveness, have been demonstrated in Korean population. The Easy Asthma Management (EAM) program, a computer-assisted asthma management program, is anticipated to facilitate the achievement of more successful clinical outcomes by filling the gaps between guidelines and actual practices. The integration of these multi-disciplinary allergy research resources and translation of scientific achievements to the bedside and society will lead to better allergy and asthma control in Korea.

Key Words: Allergy, asthma, Korea
first Korean allergy congress was held on the topic of pollen allergies in Seoul. Since then, Korean allergy congresses have been held continuously in the spring and autumn biannually (Fig. 1B). The first allergy clinic was opened in Seoul National University Hospital (SNUH) in 1979 (Fig. 1C) and the allergy division in the department of internal medicine at SNUH was launched as an independent division for the first time in Korea in 1980. KAAACI joined the Korean Federation of Science and Technology Society in 1981.

In the 1980s, the most remarkable achievement of KAAACI was the publication of an official journal, “Allergy” (The Journal of The Korean Society of Allergology; Fig. 1D). The first edition of this journal was published in 1981 with three original articles, one case report, four review articles, symposium abstracts, and newsletters. Since then, the number of submissions has increased gradually and articles have encompassed the various allergy research fields including epidemiology, occupational allergy, animal experiments, molecular biology, and immunology. The name of the journal changed to “Journal of Asthma, Allergy and Clinical Immunology” in 1998 and continues to be issued quarterly. KAAA CI and the Korean Academy of Pediatric Allergy & Respiratory Disease (KAPARD) jointly inaugurated a new journal, “Allergy, Asthma & Immunology Research” (AAIR) in October 2009. In addition to this journal, KAAA CI has published various textbooks, including Allergy in 1993, Asthma and Allergic Disease in 2002, and various clinical guidebooks (e.g. Korean...

KAAACI has communicated and had relationships with various international allergy societies and has held international congresses and joint symposiums successfully since the 1980s. KAAACI became the 27th member of the IAACI (WAO) in 1982. The first Korea-Japan joint symposium was held in Daegu, Korea in 1983. Under the leadership of professor Seok-Young Kang from Korea and professor Tatsushi Ishizaki from Japan, the first West Pacific Allergy Symposium (WPAS) was held in Kwangju, Korea in 1986. This symposium was the basis for the foundation of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI). In 1997, the 5th WPAS and the 7th Korea-Japan Joint Allergy symposium were held concurrently with the 25th Anniversary Congress of the Korean Society of Allergology (Fig. 1E). In 2000, the first Interasma North Asia/Korea Chapter was held in Seoul. In 2002, the 5th Asia Pacific Congress of Allergology and Clinical Immunology (APCACI) was held concurrently with the 7th WPAS in Seoul (Fig. 1F).

In 2003, the Korea Asthma Allergy Foundation (KAF) was launched to promote the prevention and control of asthma and allergic diseases (Fig. 1G). In 2005, KAF became a founding member of Global Alliance of Chronic Respiratory Diseases (GARD). In 2007, the second general meeting of GARD was held in Seoul, at which time GARD Korea was launched (Fig. 1H).

Fig. 2. Growth of Korean allergy SCI papers. These data were obtained from a PubMed search (keyword [allergy or asthma or hypersensitivity] and affiliation [Korea]).

Fig. 3. Prevalence of asthma and allergic diseases based on epidemiologic studies in Korea. (A) Changes in the prevalence of asthma symptoms in Korean school-aged children between 1995 and 2000. (B) Prevalence of current asthma according to age in Korean adults. (C) Prevalence of perennial allergic rhinitis, (C1) changes in prevalence between 1991 and 2001, (C2) prevalence according to age. (D) Prevalence of atopic dermatitis and food allergies based on questionnaires in Korean school-aged children.
ADVANCES IN THE FIELD

Despite a short history, scientific research by Korean allergists has expanded quantitatively and qualitatively over the last three decades since the publication of the first Korean allergy SCI paper by Kim YY et al. in 1985 (Fig. 2). Currently, many Korean allergy investigators perform global-level scientific research and lead innovative projects in various fields of allergy research.

Epidemiology

Prevalence of asthma and allergic diseases

The prevalence of asthma in Korea has been reported in several large-scale studies since the 1990s and ranges from 2% to 13% according to different methodologies, case definitions, and study populations. Nationwide surveys performed in 1995 and 2000 using the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires showed that the prevalence of asthma diagnosis in middle school-aged children (12-15 years old) increased from 2.7% in 1995 to 5.3% in 2000 (Fig. 3A). During childhood, body mass index, passive smoking, living with a dog or cat, and residence in a large city were associated with a higher risk of wheezing. An epidemiologic study based on questionnaires and methacholine provocation tests in 7- to 19-year-old subjects in urban cities revealed that the prevalence of asthma was 4.6%. The prevalence of adult asthma based on the questionnaires and methacholine challenge tests increased according to increase of age, and interestingly, asthma prevalence was unexpectedly higher in the elderly group (2.0% in <40-year-old, 3.8% in 40- to 54-year-old, 7.7% in 55- to 64-year-old, 12.7% in >65-year-old; Fig. 3B). The prevalence of perennial allergic rhinitis as diagnosed using clinical history and skin test (or MAST, RAST) to common inhalant allergen was 3.93%. The highest values (6.02%) were observed in teenagers (10- to 19-year-old; Fig. 3C). The prevalence of atopic dermatitis also increased from 7.3% in 1995 to 10.7% in 2000 in 6- to 12-year-old and from 3.9% in 1995 to 6.1% in 2000 in 12- to 15-year-old children (Fig. 3D).

Allergens and occupational allergens in Korea

Based on a nationwide survey, the most common inhalant allergens in Korea include the house dust mite (Dermatophagoides pteronyssinus, Dermatophagoides farinae), Tyrophagus putrescentiae, outdoor spider mites (Tetranychus urticae, Panonychus citiri), outdoor molds, indoor molds, cat fur, dog hair, German and American cockroaches, tree pollens, mugwort, and Japanese hop pollen. Geographical differences were observed and the sensitization rates of Japanese cedar pollen and Panonychus citiri were especially high in the Jeju province, a southern island of Korea.

Several important inhalant allergens have been reported in Korea. Outdoor spider mites, such as the citrus red mite (CRM; P. citiri), European red mite (ERM; P. ulmi), and two-spotted spider mite (TSM; T. urticae), are common allergens among fruit-cultivating farmers (Fig. 4). Specifically, CRM, first reported by Kim YK et al., are novel and important allergens that cause asthma and other allergic diseases among citrus cultivating farm and children living in rural areas. In addition, outdoor spider mites are a common sensitizing allergen associated with asthma and rhinitis symptoms in both rural and urban areas. Isocyanates including TDI, MDI, and HDI are common occupational allergens in Korea. Park HS et al., identified diisocyanate-conjugated protein and demonstrated the pathogenic role of specific IgG, as well as specific IgE, and the potential involvement of neutrophils and epithelial cells in TDI-induced asthma. Reactive dyes, herbal dusts such as ginseng and sanyak, deer hair and shell dust have been reported as unique occupational allergens in Korea.

Asthma burden

The death rate from chronic lower respiratory diseases including asthma between 1992 and 2007 increased from 12.9 (seventh leading cause of death) to 15.3 (sixth) deaths per 100,000 people.

Fig. 4. Outdoor spider mites as novel allergens that cause asthma and allergic rhinitis as shown on the cover papers of international allergy journals.

Fig. 5. Mortality rate and leading causes of death in Korea: changes between 1992 and 2007.
example (Fig. 5). Data from the Korean National Statistical Office and National Health Insurance Center (NHIC) suggest a growing economic burden of allergic diseases. The cost of asthma was estimated at over two billion dollars (the sum of direct and indirect costs) based on NHIC data and National survey on Health and Nutrition data in 2004 (Table 1).

Table 1. Socioeconomic burden of asthma in Korea (unit: million dollars)

<table>
<thead>
<tr>
<th></th>
<th>HIRA data</th>
<th>NHIC data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct cost</td>
<td>573</td>
<td>962</td>
</tr>
<tr>
<td>Indirect cost</td>
<td>538</td>
<td>1,086</td>
</tr>
<tr>
<td>Intangible cost*</td>
<td>948</td>
<td>2,066</td>
</tr>
<tr>
<td>Direct+Indirect</td>
<td>1,112</td>
<td>2,048</td>
</tr>
<tr>
<td>Total</td>
<td>2,059</td>
<td>4,114</td>
</tr>
</tbody>
</table>

HIRA, Health Insurance Review & Assessment Service; NHIC, National Health Insurance Cooperation.
*Intangible cost means willingness to pay (WTP) for a month (not a year). WTP is usually evaluated higher than true value, but it is unclear how much is appropriate.

Translational research
Recently, numerous bidirectional translational investigations (bench to bedside and bedside to bench) on asthma and allergic diseases have been reported and are underway in Korea. Various studies using patient samples including blood, sputum, and tissue, and animal studies using allergic disease models, transgenic mice, and knockout mice are being performed to elucidate the pathogenesis of asthma and allergy, mechanisms of airway inflammation and remodeling, and new therapeutic modalities for asthma and allergy.

Pathogenesis of asthma and allergy
Pathologic findings from bronchial biopsy specimens of asthmatics investigated by Cho SH et al., revealed that airway inflammation and remodeling, such as loss of epithelial cells, infiltration of inflammatory cells (especially eosinophil), and increased subepithelial collagen deposition determines the severity of asthma. This study provides the valuable information that airway inflammation and remodeling are major pathologic features of asthma and are closely related to asthma severity.

Park CS et al., investigated the survival and apoptosis of eos-
been confirmed through in vivo animal studies.\textsuperscript{35,36} which has been demonstrated in epidemiologic studies, has also (current wheezing, 9.0%; AHR 7.5%).\textsuperscript{34} The role of air pollution, (AHR; 12.2%) in industrial areas compared to residential areas industrialized urban city Yeocheon showed a higher prevalence hood asthma prevalence studies that were performed in the in- ma development have also been vigorously investigated. Child-

Air pollution and infection in asthma pathogenesis

Various types of asthma animal models expressing the heterogenous features of the human asthma phenotype have been developed and used for identifying the immunologic mechanism underlying asthma and evaluating the functional role of pathogenic molecules.\textsuperscript{31-33} Specifically, new animal models that are sensitized with allergens and natural environmental adjuvant factors via the intranasal route, not the intraperitoneal route, are pathophysiologically relevant and show similar characteristics to human allergen exposure and sensitization. Experimental asthma models of different phenotypes according to exposed levels of lipopolysaccharide (LPS) or double-stranded RNA (ds-RNA) have led to a new paradigm of asthma pathogenesis, in which both Th1 and Th2 inflammation are involved.\textsuperscript{31,32} These results also suggest a crucial role of the innate immune system in allergic airway inflammation and immune tolerance breakdown. Furthermore, studies examining mice deficient in toll-like receptor (TLR) 3, IL-13, IL-4, signal transducer and activator of transcription (STAT) 6, IFN-γ, and T-box expressed in T cells (T-box) have elucidated the underlying pathophysiologic mechanisms of allergic lung inflammation development (Th1 and Th2 inflammation).\textsuperscript{35} In these studies, the exposed doses of LPS and ds-RNA were an important factor in determining asthma phenotype; the high-dose LPS or ds-RNA model showed asthma features in which IFN-γ and Th1 inflammation were dominant (Fig. 6). In fact, cytokine analysis of sputum from non-eosinophilic severe asthmatics showed enhanced IFN-γ mRNA expression, but not enhanced IL-4 expression.\textsuperscript{31}

Air pollution and infection in asthma pathogenesis

The effects of air pollution and respiratory infections on asthma development have also been vigorously investigated. Childhood asthma prevalence studies that were performed in the industrialized urban city Yecheon showed a higher prevalence of current wheezing (18.8%) and airway hyperresponsiveness (AHR; 12.2%) in industrial areas compared to residential areas (current wheezing, 9.0%; AHR 7.5%).\textsuperscript{34} The role of air pollution, which has been demonstrated in epidemiologic studies, has also been confirmed through in vivo animal studies.\textsuperscript{35,36} In a study by Park JK et al., repeated exposure to low-dose sulfur dioxide (SO2) in an ovalbumin (OVA)-induced asthma guinea pig model led to enhanced AHR and airway inflammation.\textsuperscript{35} This study indicated that exposure to air pollution, such as SO2, may lead to asthmatic reactions by enhancing sensitization to allergens. Jang AS et al.,\textsuperscript{36} investigated the effects of ozone and diesel exhaust particulates (DEP) on asthma development and aggravation using an OVA-induced-asthma mouse model and found that the OVA-sensitized-challenged mouse exposed to ozone and DEP showed higher AHR and IL-4 and lower IFN-γ levels in BAL fluid than the control and single exposure groups; co-exposure of ozone and DEP was suggested to have an additive effect on AHR by amplifying airway Th2 inflammation.\textsuperscript{36} LPS, a cell wall component of Gram-negative bacteria, and ds-RNA, which is produced by many viruses and causes respiratory infection, are frequently encountered molecules in the environment. Experiments in asthma animal models using LPS or ds-RNA co-exposure with the allergens mentioned above have shown that respiratory infection and environmental factors are closely related to the development of asthma. In addition, the innate immune system plays a pivotal role in immunologic breakdown during asthma pathogenesis.\textsuperscript{31,32} The effects of viral infection, such as rhinovirus infection and respiratory syncytial virus (RSV) infection, on asthma development and exacerbation are also under investigation by several Korean researchers.

New therapeutic modalities for asthma and allergies

New therapeutic modalities through immunologic modulation including CpG oligodeoxynucleotides (CpG-ODNs)\textsuperscript{37} and recombinant basic fibroblast growth factor 2 (FGF2)\textsuperscript{38} have been investigated in asthma mouse models. Oligodeoxynucleotides containing a CpG motif are considered promising candidates for immune modulation in asthma because they are potent inductors of Th1 immunity, enhance the production of IFN-γ from OVA-specific T cells, and prevent the development of asthma in terms of AHR, airway eosinophilia, and OVA-specific IgE responses.\textsuperscript{37} Therefore, they are anticipated to provide an effective method for immune modulation of Th2 allergic asthma. Kim YK et al.,\textsuperscript{38} evaluated the biological roles of FGF2 in transforming growth factor-beta1 (TGF-β1) over-expressing mice and the therapeutic effects of recombinant FGF2 in the development of asthma. AHR decreased in TGF-β1 TG (+) mice and was accompanied by the up-regulation of FGF2 mRNA expression in the lung. However, AHR was markedly enhanced in TGF-β1 (+) mice with homozgyous FGF2 gene disruption. In this asthma mouse model, AHR, mucus production, and lung inflammation were inhibited markedly by rFGF2 treatment.\textsuperscript{38} These data suggest that FGF2 is a key inhibitor in the development of AHR, and rFGF2 treatment constrains the development of asthma phenotypes.

Responsiveness to corticosteroids and the role of TNF-α in Clamydia pneumonia infection was investigated by Cho YS et al.,\textsuperscript{39} C. pneumoniae infection enhanced the proliferation and survival of immune and inflammatory cells and resulted in steroid resistance. These phenomena were reversed by the addition of a TNF-α inhibitor. These results suggest that TNF-α may play an important role in steroid resistance induced by atypical micro-
bial respiratory infection. TNF-α inhibitors are therefore a candidate agent for managing steroid-resistant severe asthma. The cytoplasmic domain of CTLA-4, a negative regulator of T-cell activation, shows effective immunosuppressive properties that may be of potential use in the treatment of allergic asthma; its intranasal administration resulted in markedly reduced infiltration of inflammatory cells, secretion of Th2 cytokines, serum IgE levels, and AHR in a mouse model of allergic airway inflammation.40

Genetic research

Genetic studies of asthma and allergy susceptibility in Korea have been conducted through positional cloning and candidate gene association studies.41 Genome-wide association studies are being performed to elucidate genetic factors underlying asthma pathogenesis.42

Genetic studies for asthma and asthma-related phenotypes

Many genes and genetic polymorphisms associated with asthma and asthma-related phenotypes, such as atopy, IgE production, and AHR, were discovered by Korean allergy researchers. The genetic association of ADAM33 (disintegrin and metalloproteinase domain-containing protein 33 encoding gene), an asthma susceptibility gene, was replicated in a Korean population.43 The presence of the ADAM33 protein in bronchoalveolar lavage (BAL) fluids of asthmatics is associated with asthma development, and ADAM protein levels are related to asthma severity.44 The TNFA, IL3, IL5RA, CXCR3, PTGER3, PPARG, and eotaxin1 genes are also associated with asthma development.45-51 IL3, VEGFR2, and FCERIB genes show an association with atopy,46,52,53 and TNFA, RUNX1, and CD40 genes show an association with serum IgE production in asthma patients.45,54,55 In addition, FCERIB, TNFA, and RANTES genes are associated with AHR.56-58

The combined effects of genes such as TNFA+IL13 and TNFA+CD14 on asthma susceptibility suggest that gene-gene interactions are involved in the pathogenic mechanisms of asthma.57-60 Multi-locus analysis using multifactor-dimensionality reduction (MDR) has also shown that gene-gene or gene-environmental interactions contribute to the development of allergy and asthma.61,62

Pharmacogenomic studies

The realization of personalized and tailored medicine is anticipated in the near future. Pharmacogenomics research will make it feasible to predict drug responses and adverse reactions of individuals. Pharmacogenomic research is mainly performed in the field of respiratory therapeutic drugs (bronchodilator, anti-leukotrienes, theophylline, and corticosteroids) and adverse drug reactions (antibiotics, aspirin, allopurinol, and anticonvulsant). The B2 adrenergic receptor gene (ADRB2) polymorphism is associated with anticholinergics (tiotropium) responses, as well as β2 agonist responses.62,63 In addition, the TBXA2R gene is associated with leukotriene receptor antagonism in Korean children with asthma.64

Genetic associations and gene markers for aspirin intolerance, including HLA-DPBI*0301, HLA-DB1*0609, ALOX5, CYSLT, PGE2, TBXA2R, and FCER1A were identified in a Korean population by Park HS et al.65 Recently, the genetic interaction of CD40 and CD40L, which are co-stimulatory danger-signal molecules of T cell activation, was reported to be associated with antibiotic-associated cutaneous hypersensitivity reactions.66

Clinical studies

Large-scale, multi-center cohort studies for asthma such as COREA (Cohort for Reality and Evolution of adult Asthma),67 elderly asthma cohorts, and childhood asthma cohorts have been designed since the early 2000s and are ongoing. Many Korean clinical researchers have participated in various international multi-center clinical trials and are involved in the clinical application of new drugs, diagnostics, and medical devices. In addition to large-scale trials, various types of clinical research, including asthma morbidity and patient insight surveys,2,68 outcome research, and investigator-initiated trials are being performed. Furthermore, Korean treatment guidelines have been developed and revised through systematic review by experts.69

Activities of allergy-related societies in Korea

Korean Academy of Asthma, Allergy and Clinical Immunology

The Korean Academy of Asthma, Allergy and Clinical Immunology (KAACAI) was founded in 1972 and consists of physicians, pediatricians, dermatologists, otorhinolaryngologists, pathologists, and researchers who are interested in allergy and clinical immunology. It started with only 58 members, but now it has grown to 1225 members. The main activities of KAAACI include research communications (annual allergy congress, research work group, seminars, and symposia), publication of the Korean Journal of Allergy, Asthma and Clinical Immunology, guideline development, and educational workshops and lectures. In addition, the group has organized international communications such as joint meetings with the World Allergy Congress (WAC), Asia Pacific Congress of Allergy and Clinical Immunology (APCACI), West Pacific Allergy Symposium (WPAS), Interasma, and Korea-Japan Joint Allergy Symposium.

Korea Asthma Allergy Foundation

The Korea Asthma Allergy Foundation (KAF) was founded for the purpose of supporting academic and research activities, public relations, and education related to the prevention of asthma and allergy. In addition, the KAF acts to promote the quality of life and health outcomes of patients. The main activities of the KAF include public relations (TV, newspaper, and magazine campaigns, World Asthma Day ceremony, seminars, and con-
ventions on asthma/allergic diseases), education (patient education, asthma-friendly schools), research (burden of asthma, asthma morbidity and patient insight survey, guideline implementation) and international relationships as an active member of GARD. KAF contributed greatly to focussing the government’s attention on asthma and allergic diseases, and the organization developed the nationwide asthma and atopic disease prevention and management plan (the Korean government has provided three million dollars annually since 2008).

The development of the Easy Asthma Management (EAM) program, a computer-assisted asthma management program, was one of the most innovative works of KAF EAM provides an easily acceptable, simplified, and practical protocol that focuses on the diagnosis, treatment, and monitoring of asthma for general practitioners. The use of EAM is anticipated to facilitate the achievement of more successful clinical outcomes by filling the gaps between guidelines and actual practices.74,75

CONCLUDING REMARKS: PERSPECTIVES OF ALLERGY IN KOREA

The research and clinical capacity to understand and treat asthma and allergic diseases in Korea were improved remarkably in a brief time. Outstanding academic and scientific research has been performed in a variety of allergy research fields, including basic immunology, genomics and pharmacogenetics, new therapeutic target discovery, and clinical medicine. These multi-disciplinary allergy research resources are being integrated to identify allergic pathogenic mechanisms and curative treatments for allergy. The future directions of allergy research in Korea will focus on the pathogenic mechanisms of allergy (mechanisms of immunologic tolerance breakdown, the impact of the environment and climate change, role of extracellular vesicles in the development of allergy), the development of new therapeutic modalities (discovery of new therapeutic targets and immune modulation), and the realization of personalized medicine. The translation of scientific achievements to the bedside and society through the collaboration of researchers and health promotion activities will lead to better allergy and asthma control in Korea.

REFERENCES


51. Oh SH, Park SM, Lee YH, Cha JY, Lee JY, Shin EK, Park JS, Park BL, Shin HD, Park CS. Association of peroxisome proliferator-activated...


