Message from the President

Dr. Tak-Hong Lee

CBE, MD, ScD, FRCP, FRCPath, FHKCP
Specialist in Immunology and Allergy
President, Hong Kong Institute of Allergy

I am very grateful to our Editor, Dr. Jane Chan, and her team in producing this second six-monthly newsletter in such a timely manner. This issue is full of interesting articles which I hope you will enjoy.

Dr. Chan will explain in greater detail that we have enlisted the help of a group of sub-editors for this issue, whose role was to identify and provide a short commentary of recent important publications in their respective thematic area. It is hoped that this approach will provide a broader and more comprehensive overview of key discoveries for the entire discipline.

Many colleagues have contacted us to say how much they enjoyed reading the first newsletter and encouraged us to circulate future ones more widely. Therefore we have decided to email this new issue and the previous one to all the Hong Kong doctors in MIMS extensive database. This is why you may have received the newsletters even if you are not a member of The Hong Kong Institute of Allergy (HKIA). We are grateful to Menarini for its support to produce this issue and to 'e-blast' both newsletters to colleagues.

If you would like to receive our future newsletters, please join HKIA by completing the attached simple application form and returning it to Ms. Sigourney Liu as indicated. One of us on Council will sponsor you. Please make sure you provide us with a clear contact email address. There is no joining subscription as Council has decided to waive the once-off fee until December 2016.

HKIA was incorporated in February 1996 by a group of Allergists, Chest Physicians, Paediatricians, Otorhinolaryngologists and Dermatologists, to promote the discipline of allergy. It is the only professional society in HK dedicated to allergy. Our Patron is Dr. Ko Wing-man, Secretary for Food and Health in The Government of Hong Kong Special Administrative Region.

HKIA's mission is to:

- *Increase allergies' public and professional profile;*
- *Create more opportunities for training of aspiring allergists and allied health professionals;*
- *Promote an environment to facilitate discovery of new knowledge;*
- *Progress an agenda to help improve allergy services.*

HKIA has a number of active subcommittees that include:

- *Scientific Programme and Research (co-chair: Prof. Ting-Fan Leung and Prof. Gary Wong)*
- *Public Engagement (co-chair: Dr. Henry Chan and Dr. Marco Ho)*
- *Publication (chair: Dr. Jane Chan)*
- *Social Programme (co-chair: Dr. Robert Tseng and Dr Gilbert Chua)*
- *Membership (co-chair: Dr. Johnny Chan and Dr. Kit-Man Sin)*
- *Education, Training and Fellowships (co-chair: Dr. Fanny Ko and Dr. Adrian Wu)*
- *Immunology (co-chair: Dr. Eric Chan and Dr. Roland Leung)*
- *Service Development (co-chair: Dr. Tak-Hong Lee and Dr. Christopher Lai)*
- *Allied Health Professionals and Health Promotion (co-chair: Ms. June Chan and Ms. Maggie Lit)*
- *Finance (co-chair: Dr. Alice Ho and Dr. Tak-Fu Tse)*

The benefits of membership include being part of a community of like-minded colleagues in a vibrant specialty that is trying to push forward the frontiers of current allergy healthcare in HK; receipt of regular newsletters; eligible to apply for grants to attend allergy-related conferences and study visits abroad; eligible to apply for small pump priming research grants for pilot studies to obtain preliminary data; eligible for discounted fees to attend workshops and conventions organized by HKIA; invitation to social activities; and until Dec 2016 it is free to join.

I hope you will enjoy reading this issue of our newsletter and that you will take this golden opportunity to become a member of HKIA.

Dr. Lee Tak-Hong
President
Hong Kong Institute of Allergy

Message from the Editor

Dr. Jane Chun-Kwong Chan

MD (U Chicago), FHKCP, FHKAM (Medicine), American Board of Internal Medicine (Pulmonary Disease), PDipID (HK)
Specialist in Respiratory Medicine

This second issue of the HKIA Newsletter has undergone two major changes since our earlier issue. The first change is related to the increased number of "corners" or sections intended to reflect the multitude of disciplines and topics relevant to allergy and immunology. In this issue, the following seven Sections/Corners have been established: Air Pollution, Asthma, Ear Nose and Throat, Food Allergy, Skin Allergy, Drug Allergy/Immunology, and General Allergy. The second change is the direct result of the foresight of our President Dr. Tak-Hong Lee, who saw the need to engage a broader group of healthcare professionals, especially the young aspiring opinon leaders, as Sub-editors for our Newsletter. These Sub-editors, most of whom working in the public sector, would be tasked with identifying and writing up on 1-3 recently published scientific study/studies relevant to their respective field of interest, highlighting key scientific findings while providing the necessary background discussion so as to enable our readers to gauge how such findings may impact current or future clinical practice.

Kindly meet our team of Sub-editors and their responsible Sections/Corners as shown below:

Sub-editors	Name	Specialty
Air Pollution	Dr. Jane Chun-Kwong Chan	Respiratory Medicine
	Dr. Kwok-Chu Kwong	Respiratory Medicine
Asthma	Dr. Veronica Lee Chan	Respiratory Medicine
	Dr. Lai-Yun Ng	Respiratory Medicine
Ear Nose & Throat	Dr. Ambrose Chung-Wai Ho	Otorhinolaryngology
	Dr. Jacky Lam	Otorhinolaryngology
	Dr. Pui-Yee Lo	Otorhinolaryngology
Food Allergy	Dr. Alfred Yat-Cheung Tam	Paediatrics
	Dr. Marco Hok-Kung Ho	Paediatric Immunology and Infectious Diseases
Skin Allergy	Dr. Johnny Chun-Yin Chan	Dermatology and Venereology
Immunology/Drug Allergy	Dr. Eric Yuk-Tat Chan	Immunology
	Dr. Temy Mo-Yin Mok	Rheumatology
General Allergy	Dr. Tak-Hong Lee	Immunology and Allergy
	Dr. Alson Wai-Ming Chan	Paediatrics
	Ms. Maggie Pik-Kee Lit	Advanced Practice Nurse, Medicine

It is hoped that with such diverse group of Sub-editors, our Newsletter would serve to link up all relevant practitioners and to drive up increasing professional interest in coming together as a family of advocates in advancing the field of Allergy and immunology.

Dr. Jane Chun-Kwong Chan
Editor, HKIA e-newsletter
Hong Kong Institute of Allergy

Outdoor air pollution: Regional differences on a global scale

Dr. Jane Chun-Kwong Chan

MD (U Chicago), FHKCP, FHKAM (Medicine), American Board of Internal Medicine (Pulmonary Disease), PDipID (HK)
Specialist in Respiratory Medicine

Landmark study on outdoor air pollution sources

Air pollution has been associated with many health hazards: the association of chronic obstructive pulmonary disease (COPD) with ozone, and the association of acute lower respiratory illness, cerebrovascular disease, ischemic heart disease, COPD and lung cancer with $PM_{2.5}$ (fine particulate matter with diameter < 2.5 micron)[1]. A study just e-published in Nature[2], which calculated air pollution-related mortality based on the method of the global burden of disease for 2010, reported that outdoor air pollution, mostly by $PM_{2.5}$, leads to 3.3 (95% CI: 1.61-4.81) million (m) premature deaths per year worldwide, more than combined deaths from malaria and HIV/AIDS. The authors warn that unless action is taken, the number of deaths, currently at six deaths per minute, will double by 2050.

The study was conducted jointly by chemistry and public health scientists in Germany, Cyprus, USA, and Saudi Arabia, and is the first ever study which singles out different outdoor air pollution sources and estimates the number of premature deaths they each cause. The researchers used a complex model to investigate the link between premature mortality and 7 emission source categories, including (1) residential and commercial energy (wood and coal burning for heating homes and cooking; waste disposal and diesel generators), (2) agriculture (ammonia is released from fertilizer use and domesticated animals; ammonia in turn can spur formation of $PM_{2.5}$), (3) natural sources, (4) power generation (by fossil fuel fired power plants), (5) industry, (6) biomass burning and (7) land traffic.

The combination of high per capita mortality with high population density has rendered China, C, to rank top as the country with the most number of premature mortality (1.36 m) linked to outdoor air pollution, followed by India, I, (0.65 m, ranking 2nd), Pakistan, P, (0.11 m, ranking 3rd) and Bangladesh, B, (0.092 m, ranking 4th). Russia ranked 6th, USA 7th, Germany 12th, and Japan 15th (all under 0.01 m). There was clearly a difference in the sources of outdoor air pollution between the 4 top ranking countries, which were all in Asia, and 4 more developed countries as exemplified by Russia (R), USA (U), Germany (G) and Japan (J):

Emission source	Contribution to global annual premature deaths, %	Contribution to annual premature deaths in top ranking countries (%)	Contribution to annual premature deaths in more developed countries (%)
Residential and commercial energy	59	C (76), I (77), P (67), B (78)	R (18), U (12), G (17), J (29)
Agriculture	7	C (7), I (1), P (1), B (2)	R (26), U (17), G (26), J (22)
Power generation	7	C (7), I (5), P (1), B (6)	R (17), U (19), G (10), J (15)
Industry	3	C (3), I (3), P (2), B (2)	R (5), U (5), G (8), J (14)
Biomass burning	8	C (2), I (9), P (3), B (8)	R (21), U (9), G (3), J (8)
Land traffic	5	C (2), I (4), P (3), B (4)	R (13), U (36), G (36), J (12)

This table shows that emissions from residential and commercial energy use, including waste disposal and diesel generators, constitute the major source of premature mortality worldwide (59%), and in Asia (67-78%), while In the U.S. and Germany, the sources of outdoor air pollution which contributed to premature mortality are, in order of decreasing mortality: land traffic (36%), agriculture (17-26%), power generation (10-19%), residential and commercial energy (12-17%), industry (5-8%), and biomass burning (3-9%).

The linearity of ambient particulate matter air pollution exposure and mortality

Further insights on the health hazards of $PM_{2.5}$ are shed by another newly e-published paper[3]. In this prospective cohort study, a 1995-6 recruited U.S. cohort of over 500,000 retired persons aged 50-71 were followed up from the beginning of 2000 (2000 being the first full year that outdoor $PM_{2.5}$ exposure data were available nationwide) to end of 2009, death or moving away, whichever of the three occurred first.

The research group found that higher levels of ambient $PM_{2.5}$ exposure were significantly associated with increased mortality due to all causes (Hazard Ratio (HR) = 1.03 per 10 ug/m^3; 95% CI: 1.00, 1.05) and cardiovascular disease (HR = 1.10; 95% CI: 1.05, 1.15). $PM_{2.5}$ exposure was significantly associated with increased risk of repiratory mortality in never smokers (HR = 1.27; 95% CI: 1.03, 1.56). Although these findings echo earlier findings from a similarly large US cohort which were followed up from 1982 through 1998, the mean study period $PM_{2.5}$ level was significantly lower at 12.2 ug/m^3 in this new study as compared to the mean study period $PM_{2.5}$ level of 17.7 ug/m^3 in the 1990s study. This implies despite significant improvement in ambient air quality as a result of measures to curb air pollution, health threats have remained unchanged! In other words, the relationship between $PM_{2.5}$ levels and health hazards rides on a strictly linear curve and no levels should be considered acceptable.

Reality check on Hong Kong

To put these figures in Hong Kong's perspective, the annual $PM_{2.5}$ levels locally were 25-43 ug/m^3 in 2012[4], while the annual $PM_{2.5}$ level in Beijing was 98.5 ug/m^3 in 2013, the Chinese national reference being at 35 ug/m^3 [5]. Hong Kong, a well-developed city with close geographic proximity to Greater China, would benefit from more detailed computer modelling and large scale epidemiological research to discover the main sources of outdoor air pollution and the effects of each pollutant on health outcomes so that the problem can be tackled more effectively.

References

1. Burnett RT et al. Integrated risk function for estimating the Global Burden of Disease attributable to ambient fine particulate matter exposure. Environ Health Perspect 2014; 122: 397-403.
2. Lelieveld J et al. The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature 2015; 525: 367-371 (doi: 10.1038/nature15371).
3. Thurston GD et al Ambient particulate matter air pollution exposure and mortality in the NIH-AARP diet and health cohort. Environ Health Perspect 2015 (http://dx.doi.org/10.1289/ehp/1509676).
4. http://www.aqhi.gov.hk/api_history/english/report/files/AQR2012e_final.pdf).
5. http://www.globaltimes.cn/content/838375.shtml.

Indoor air pollution and health hazards

Dr. Kwok-Chu Kwong

MBBS(HK), MRCP(UK), FRCP(Edin & Glasg), FHKCP, FHKAM
Specialist in Respiratory Medicine
Senior Medical Officer, Department of Medicine & Geriatrics, Princess Margaret Hospital

The importance of good indoor air quality for the health of the individual was recognized as long ago as 150 years past. Here two studies on indoor air pollution are discussed: one on possible tools to assess the residential environment for children with atopic dermatitis[1], and the other on the entity called "Sick Building Syndrome[2]."

Exacerbation of symptoms of atopic dermatitis by indoor air pollutants

Given that atopic Dermatitis [AD] is most prevalent in infants and young children, and that they spend most of their time indoors, due attention needs to be paid to indoor air quality for AD patients. Past studies have invoked indoor air pollution as an aggravating factor in AD. These air pollutants probably induced oxidative stress in the skin, leading to skin barrier dysfunction or immune dysregulation. An earlier epidemiological study[3] involving 2536 children examined the effect of indoor exposure on eczema and allergic symptoms. Exposure emissions due to redecoration activities seemed to be associated with risk of eczema and allergic symptoms. In a subsequent study, improvement in AD severity was shown in 425 kindergarten children after reducing indoor air pollutants[4].

Residential environment may help to decipher type of indoor air pollutants

A recent study[1] of 150 children (age 2-168 months) with AD living in Seoul, Korea, has set out not to verify the well-researched causality between indoor air pollution and exacerbation of AD symptoms but to investigate the relationship between indoor air pollutant levels and residential environment. Indoor air pollutants measured included PM_{10} (particulate matter with diameter < 10 micron), formaldehyde, carbon dioxide (CO_2) and monoxide, nitrogen dioxide (NO_2), total volatile organic compound (TVOC), benzenes, toluene, xylene, styrene, bacterial aerosols and airborne fungi. Residential environment was assessed by question-naires completed by the children's parents.

Significantly high concentration of PM_{10} was related with visible mold on the walls. As PM includes particles from fungi[5], removal of visible mold might be helpful to lower indoor PM_{10} concentration. The level of formaldehyde increased in cases of moving to a newly-built building or a renovated house. Paradoxically, the use of artificial air freshener was significantly associated with high concentrations of benzenes, toluene and TVOC. Xylene level was significantly high when oil was used as heating fuel. Styrene levels were significantly high in a mixed residential and commercial complex building. The indoor concentration of bacterial aerosols was significantly low with the use of air cleaner. High NO_2 and benzene concentrations were present in case of almost no ventilation.

To alleviate AD symptoms, simple questions about residential environments, such as visible fungus on the walls and the use of artificial air freshener, are helpful to assess possible increased indoor air pollutant levels when direct measurement is not available.

Sick building syndrome

Energy crisis in 1973 led to smaller residential and office building with lower air changes. This resulted in development of Sick Building Syndrome [SBS]. Sick building syndrome consists of a group of mucosal, skin, and general symptoms that are temporally related to working in particular buildings. It is the workers who are symptomatic, but the building or its services constitutes the cause. A large two-year prospective study of junior high schoolers in Taiyuan, Shanxi Province in China[2] examined associations between environmental parameters such as room temperature, relative air humidity (RH), CO_2, NO_2, sulphur dioxide (SO_2), ozone (O_3) and PM_{10}, and health outcomes including prevalence, incidence and remission of SBS symptoms. Taiyuan is a heavily industrialized area relying on coal combustion. The city is surrounded by mountains and has heavy outdoor air pollution especially by SO_2 and particulate matter, most notably during the heating season.

Totally 2134 pupils participated at baseline, and 1325 stayed in the same classrooms during the study period (2010–2012). At baseline, both indoor and outdoor SO_2 were found positively associated with prevalence of school-related symptoms (symptoms which improved when away from school), and indoor O_3 with prevalence of skin symptoms. At follow-up 2 years later, the prevalence of mucosal symptoms, general symptoms and school-related symptoms had increased. Various air pollutants were found to be positively associated with new onset of the following symptom clusters:

Indoor PM_{10},: :skin, mucosal and general symptoms
Indoor CO_2 and RH : mucosal, general and school-related symptoms
Outdoor NO_2 & PM_{10} : skin, general and mucosal symptoms, and school-related symptoms

In conclusion, environmental pollution, including PM_{10}, SO_2 and NO_2, could increase the prevalence and incidence of SBS and decrease the remission rate.

Despite measures taken by the local government and environmental protection agency in Shanxi province to reduce level of SO_2 and particulate matters in the past decade, the levels of NO_2, a pollutant mainly coming from vehicle exhaust, had remained high without change over a 6-year period from 2006 to 2012. Findings from the current study echo those of a 2004-2006 study by the same investigator[6], suggesting persistent health hazards of environmental air pollution for that community.

Mortality from indoor air pollution

Unfortunately, indoor air pollution could have much more serious adverse health effect other than skin problem or SBS. According to WHO, nearly 50% of the death among children caused by acute respiratory infection was due to indoor air pollution. Exposure to indoor pollution may be responsible to nearly 2 million deaths per year in developing countries. Thus indoor air pollution could have adverse health effect ranging from simple skin aging[7]; persistent cough[8] to life-threatening illness[9].

References

1. JH Lee et al. Relationship Between Indoor Air Pollutant Levels and Residential Environment in Children With Atopic Dermatitis. Allergy Asthma Immunol Res. 2014 November;6(6):517-524.
2. Xin Zhang et al. A Longitudinal Study of Sick Building Syndrome (SBS) among Pupils in Relation to SO2, NO2, O3 and PM10 in Schools in China. PLoS One. 2014; 9(11): e112933. Published online 2014 Nov 14. doi: 10.1371/journal.pone.0112933.
3. Herbarth O et al. Association between indoor renovation and eczema in early childhood. International Journal of Hygiene & Environmental Health 2006; 209(3):241-7.
4. Kim HO et al. Improvement of atopic dermatitis after reducing indoor air pollutants. Annals of Dermatology 2013;25(3):292-7.
5. Jenerowicz D et al. Environmental factors and allergic diseases. Ann Agric Environ Med 2012;19:475-81.
6. Zhang X et al. The prevalence and incidence of sick building syndrome in Chinese pupils in relation to the school environment: a two year follow up study. Indoor air 2011;21:462–471.
7. Li M et al. epidemiological evidence that indoor air pollution from cooking with solid fuels accelerates skin aging in Chinese women. Journal of Dermatological Science 2015;79(2):148-54.
8. Liu MM et al. Effects of outdoor and indoor air pollution on respiratory health of Chinese children from 50 kindergartens. Journal of Epidemiology 2013;23(4):280-7.
9. Upadhyay AK et al. Impact of indoor air pollution from the use of solid fuels on the incidence of life threatening respiratory illness in children in India. BMC Public Health 2015;15:300.

Potential therapeutic targets of allergic asthma

Dr. Veronica Lee Chan

MBChB, MRCP(UK), FHKAM
Specialist in Respiratory Medicine
Associate Consultant, Department of Medicine & Geriatrics, United Christian Hospital

Severe refractory asthma refers to patients with uncontrolled symptoms, despite high-intensity treatment according to international guidelines, and adequate exclusion of alternative diagnosis, poor compliance, ongoing allergen exposure and co-morbidities[1]. This accounts for approximately 10% of patients with asthma and is associated with substantial morbidity and mortality and a large fraction of health care costs. Pathophysiology of severe refractory asthma is characterized by persistent airway inflammation and marked airway remodeling, driven by T helper 2 (Th2) cell-mediated inflammation, producing the cytokines interkukin-4 (IL-4), interlukin-5 (IL-5), IL-9, and IL-13. This results in eosinophilic infiltration of the airways and B-cell release of antigen-specific immunoglobulin E (IgE)[2].

Treatment of this group of patients is an unmet need. Monoclonal antibodies, such as omalizumab that are directed against the high affinity Fcε receptor I (FcεRI) domain of circulating IgE, had been shown to reduce the rate of exacerbation in moderate/severe asthma. But the response rate to omalizumab is variable and difficult to predict, reflecting a tremendous heterogeneity in advanced disease. Clearly other drugs are required to manage these patients with severe asthma. It is therefore encouraging that several recent reports suggest that finally a group of new drugs may be on the horizon that could be useful in refractory asthma.

MEPOLIZUMAB

Mepolizumab is a human monoclonal antibody against IL-5. Last year, two multi-center, randomized, placebo-controlled phase III trials on Mepolizumab to treat severe eosinophilic asthma were published in the New England Journal of Medicine.

Ortega HG et al[3] recruited asthmatic patients (age between 12 and 82 years of age) with at least two asthma exacerbations in the previous year requiring systemic glucocorticoids while they were receiving high dose inhaled corticosteroid (at least 880μg of fluticasone propionate or the equivalent), and elevated blood eosinophil count. Patients were randomly assigned to receive Mepolizumab, administered as either a 75-mg intravenous route or a 100-mg subcutaneous route, or placebo every 4 weeks for 32 weeks. Exacerbations necessitating an emergency department visit or hospitalization were reduced by 32% in the group receiving intravenous mepolizumab and by 61% in the group receiving subcutaneous mepolizumab. Treatment with mepolizumab was also associated with increase in FEV1, improvement in St George's Respiratory Questionnaire (SGRQ), and improvement in Asthma Control Questionnaire (ACQ-5).

Bel EH et al[4] recruited patients with severe persistent asthma taking maintenance systemic glucocorticoids (5 to 35mg per day of prednisolone or its equivalent) despite high-dose inhaled glucocorticoids and an additional controller. The patients also needed to have elevated blood eosinophil count. The doses of oral glucocorticoids had been reduced as much as possible before randomization to receive either mepolizumab (at a dose of 100mg) or placebo by subcutaneous infection every 4 weeks for 20 weeks. Patients receiving subcutaneous mepolizumab had significantly greater reduction in the maintenance oral glucocorticoid dose than did those receiving placebo. Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group had a relative reduction of 32% in the annualized rate of exacerbations, and a significant reduction in asthma symptoms.

Both studies have shown mepolizumab to be safe with an acceptable side-effect profile. But there were areas of uncertainty. Firstly, both studies were relatively short in duration. Observational studies evaluating the response to the cessation of mepolizumab found that eosinophil counts in blood and sputum increased significantly, returning to pretreatment values within 3 months after mepolizumab was stopped[5]. This change was associated with a loss of asthma control, and 3 to 6 months after cessation of treatment, patients were found to have pretreatment exacerbation levels. Secondly, although serum and sputum eosinophil counts drop precipitously in the presence of monoclonal antibodies against IL-5, bronchial biopsy specimens demonstrate persistent eosinophilic infiltration[6]. IL-5 inhibition also failed to have substantial improvement in the 'traditional asthma hallmarks' including late phase reaction and airway hyperresponsiveness[7].

DUPILUMAB

Dupilumab is a fully human monoclonal antibody targeting the alpha subunit of the IL-4 receptor and blocking the downstream signaling mediated by both IL-4 and IL-13. Wenzel S et al[8] conducted a randomized, double-blind, placebo-controlled, parallel group phase 2A study in 28 sites in the United States, in patients having persistent, moderate-to-severe asthma, and elevated blood eosinophil count or sputum eosinophil level despite medium-dose to high-dose inhaled corticosteroids (ICS) plus long-acting beta-agonist (LABAs). Patients were given dupilumab (300mg) or placebo subcutaneously once weekly for 12 weeks. Patients were instructed to discontinue LABAs at week 4 and to taper and discontinue ICS during week 6 through 9. This proof-of-principle study had shown a favorable response in dupilumab group, with an 87% reduction in the proportion of patients with an asthma exacerbation, significant improvement in lung function, and significant reduction of biomarkers associated with Th2-driven inflammation, while withdrawing ICS and LABAs. But we have to interpret the results very carefully[9]. Firstly, the study results can only be applied to a subpopulation of asthmatic patients with elevated eosinophil levels. Secondly, withdrawal of LABAs and/or ICS in patients with persistent asthma is very rarely practiced in the real world situation. Indeed, in the first phase of the trial, while all patients were using ICS and LABAs, there was no significant difference in exacerbations between the dupilumab and the placebo group. Thirdly, injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo. Longer studies comparing dupilumab with placebo as add-on therapy to ICS and LABAs without withdrawal are needed to show the clinical usefulness and durability of this drug.

Up till now, most attention seems to focus on asthma endotypes exhibiting Th2-mediated airway inflammation with blood or sputum eosinophilia. However, recent research suggests that a proportion of severe asthma patients may suffer from steroid unresponsive neutrophilic airway inflammation mediated by Th1, Th9 and Th17 directed pathways[10]. Moreover, blockade of a single cytokine often results in only partial efficacy, and does not address all the aspects of asthma. There is an urgent need to target the root cause of the disease.

CALCILYTICS

A recent paper published in the prestigious peer-reviewed journal Science Translational Medicine on calcilytics as a potential asthma treatment[11] produced world-wide interest and much media publicity.

Calcilytics are negative modulators of the G-protein coupled calcium-sensing receptor (CaSR). The CaSR is the master controller of extracellular free ionized calcium ion concentration via the regulation of parathyroid hormone secretion. In addition it is expressed in blood vessels, breast and placenta where it regulates gene expression, ion channel activity and cell fate. Drugs known to block these proteins already exist. Calcilytic drugs were developed as a treatment for osteoporosis, as they increase the level of parathyroid hormone by targeting CaSRs. This helps to increase the level of calcium in the blood.

Utilising mouse models of asthma and human airway tissue taken from asthmatic and non-asthmatic people, Yarova and colleagues found three times the number of CaSRs in biopsies of smooth muscle taken from the airways of people with asthma, compared with those who do not have asthma. The same was true for the lungs of a mouse model of allergic asthma compared with healthy controls. They also showed that the positively charged eosinophil derived inflammatory proteins (eosinophilic cationic protein and a mimic of major basic protein) characteristically present in asthmatic airways stimulate CaSRs leading to an amplification of the airways inflammation. Mice that were genetically engineered to abrogate expression of airway smooth muscle CaSRs did not have an inflammatory response to the positively charged proteins. The drug calcitriol, which is used to treat osteoporosis, is known to block the actions of the receptors. The drug reduced inflammation of the airways in their mouse model of asthma. The researchers are now planning to develop a version of the drug that can be inhaled to maximize its effectiveness and minimize side effects. Human trials are planned to commence in a couple of years.

It remains unclear why people with asthma had an increased number of receptors, and if this is true for everyone with asthma. The researchers predict that if calcilytics prove to be effective in clinical trials, it will take around five years for them to become available as a treatment for asthma. Drug development will involve further animal trials to work out what dose would be required to achieve clinically meaningful results, and will also test its safety. If these trials are successful, the research will progress to human trials. This is an exciting piece of research that may provide a new treatment for asthma.

Conclusion

In the advancing era of personalized medicine, physicians need to consider characterizing in detail the endotypic pattern of each patient with severe refractory asthma, so that targeted therapeutic agents will be tailored and delivered to the 'right patient' at the 'right time'. The characterization of a Th2-high phenotype using biomarkers like FENO, blood or sputum eosinophil counts, and serum periostin may enable selection of patients for treatment with monoclonal antibodies directed against specific components of the Th2 inflammatory cascade. The understanding of Th-2 low asthma is still limited. With better understanding of pathobiological mechanisms, new potential asthma therapeutic targets may be indentified in the near future.

References

1. Bel EH et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011; 66:910-917.
2. Poon AH et al. Pathogenesis of severe asthma. Clin Exp Allergy 2012; 42:625-637.
3. Ortega HG et al. Mepolizumab Treatment in Patients with Severe Esoinophilc Asthma. N Eng J Med 2014;371:1198-1207.
4. Bel EH et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. N Eng J Med 2014;371:1189-97.
5. Haldar P et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol 2014; 133:921-923.
6. Flood-Page PT et al. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes number in asthmatic airways. Am J Respir Crit Care Med 2003; 167:199-204.
7. Nathan H et al. Monoclonal antibodies for the treatment of refractory asthma. Curr Opin Pulm Med 2014; 20:87-94.
8. Wenzel S et al. Dupilumab in persistent asthma with elevated eosinophil levels. N Eng J Med 2013;368:2455-66.
9. Michael E et al. Inhibiting Interleukin-4 and interleukin-13 in difficult-to-control asthma. N Eng J Med 2013; 368:2511-2513.
10. The ENFUMOSA study group. The ENFUMOSA cross-sectional European Multicentre study of the clinical phenotype of chronic severe asthma. Eur Respir J 2003; 22;470-477.
11. Yarova PL et al. Calcium sensing receptor antagonists abrogate airway hyperresponsiveness and inflammation in allergic asthma. Sci Transl. Med. 2015; 284ra60, 1-10.

Intranasal antihistamine as adjunct treatment for allergic rhinitis

Dr. Ambrose Chung-Wai Ho

MBBS (HK), MRCSEd, FRCSEd (ORL), FHKCORL, FHKAM (Otorhinolaryngology)
Specialist in Otorhinolaryngology
Honorary Consultant in Otorhinolaryngology, Hong Kong Sanatorium and Hospital

Dr. Jacky Wai-Kei Lam

Resident Specialist
Department of Ear Nose & Throat, Queen Mary Hospital

Dr. Pui-Yee Lo

MBChB, HKCORL
Specialist in Otorhinolaryngology
Associate Consultant, Department of Ear Nose and Throat, Queen Elizabeth Hospital

Introduction

Pharmacological management is mainstay treatment for allergic rhinitis. Oral antihistamines are commonly prescribed to provide symptomatic relief. When compared with oral antihistamines, intranasal antihistamines give the advantage of delivering a higher concentration of medication to a specific targeted area, resulting in fewer systemic adverse effects[1]. According to the 2015 Clinical Practice Guideline on allergic rhinitis published by the American Academy of Otolaryngology-Head and Neck Surgery, clinicians may offer intranasal antihistamine for patients with seasonal, perennial, or episodic allergic rhinitis[2].

Currently, azelastine (approved for ages five years and older) and olopatadine (approved for ages six years and older) are the two FDA-approved intranasal antihistamine preparations for the treatment of allergic rhinitis. In Hong Kong, only intranasal azelastine has been registered for use in the treatment of seasonal allergic rhinitis and nonallergic vasomotor rhinitis.

Pharmacology

Azelastine is a phthalazinone derivative with H1-receptor binding approximately tenfold greater than chlorpheniramine. It has demonstrated a wide range of pharmacologic effects on chemical mediators of inflammation such as leukotrienes, kinins and platelet activating factors in vitro and in vivo. As a class, the onset of action occurs within 15 minutes when applied intranasally, before any significant level of systemic absorption. The effect lasts up to four hours. The active substance is azelastine hydrochloride, which is absorbed rapidly and mainly distributed in peripheral organs, but only to a minor extent in the brain.

Efficacy and side-effects

If applied intranasally, adverse effects include a bitter aftertaste, headache, nasal irritation, and epistaxis. If taken orally, sedation and somnolence of mild to moderate intensity may occur and can potentially affect driving. It is well tolerated in adult and children 12 years of age or older.

Current trend

Recently there is a single formulation nasal spray, which consists of both the intranasal antihistamine, azelastine hydrochloride, and the intranasal corticosteroid, fluticasone propionate, in an advanced delivery system.

Systematic review of 20 studies with thousands of patients with either seasonal or perennial allergic rhinitis was performed[3.] Among those, there were 346 adult subjects who had received the combined formulation. These subjects were compared with those who had received the individual active agent components. The combined formulation was shown to provide significantly

better symptom relief than either the intranasal antihistamines or intranasal corticosteroids alone, with a greater improvement in nasal symptom score.

A long-term safety study of this new formulation was also recently reported[4]. The study was a randomized, open-label trial with 612 subjects recruited. One group (n=405) received new intra-nasal spray with formulation containing both antihistamine and corticosteroid. The other group (n=207) received intranasal corticosteroid (fluticasone propionate) only. The subjects were required to use the drugs daily even if symptoms were not bothersome. The follow up time was at least 1 year. This long-term safety study concluded that the new drug was well tolerated, with no late-occurring adverse effects such as dysgeusia, epistaxis, atrophic rhinitis or impaired glucose tolerance.

Conclusion

Intranasal antihistamines have not gained their popularity despite being an alternative in patients whose symptoms did not improve with second-generation oral antihistamines. Their use is limited by the cost and their reduced effectiveness compared with intranasal corticosteroids[5,6]. New combination formula of intranasal antihistamine and corticosteroid appears to be a safe and well tolerated option for recalcitrant rhinitis.

References

1. Bousquet J et al. ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 suppl):S147–S334.
2. Seidman MD et al. Guideline Otolaryngology Development Group. AAO-HNSF. Clinical Practice Quideline: Allergic rhinitis. Otolaryngol Head Neck Surg 2015;152(1 Suppl):S1-43.
3. Berger WE et al. Intranasal spray medications for maintenance therapy of allergic rhinitis. Am J Rhinol Allergy 2015;29(4):273-82.
4. Berger WE et al. Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis.J Allergy Clin Immunol Pract 2014;2(2):179-85.
5. Corren J et al. Azelastine Cetirizine Trial No. 1 (ACT 1) Study Group. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. Clin Ther. 2005;27(5):543–553.
6. Berger WE et al. Rhinitis Study Group. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. Ann Allergy Asthma Immunol 2003;91(2):205–11.

Short course oral egg hyposensitization may work and remain effective for a long time.

Dr. Alfred Yat-Cheung Tam

MBBS(HK), FRCP(Edin.,Lond.,Glasg.), FHKCPaed, FHKAM(Paediatrics)
Specialist in Paediatrics

Egg allergy is one of the most common food allergies in early childhood. Although many will outgrow their allergy, those children whose allergy is ongoing or persisting face a lot of inconvenience in life, especially when dealing with food at school or other public places. Egg allergy is also one of the most common causes of severe anaphylaxis, with possible life-threatening consequences. Apart from avoidance, hyposensitization has recently become a potentially important modality of treatment[1]. However, many issues are as yet unsolved: Protocols and use of allergen have yet to be standardized. Even for those children who have been successfully desensitized, continuous intake of a small amount of egg protein is necessary to maintain the hyposensitized state[2]. In order for hyposensitization to be widely practicable, there is a need for a convenient and quick protocol that may have a lasting effect without the need for continual post-sensitization challenge. This present study tries to fill this gap.

The authors of a recent study from Spain[3] reported the successful desensitization of egg allergy using an oral immunotherapy (OIT) regimen for 3 months, whose effect was maintained as demonstrated by double-blind placebo controlled food challenge (DBPCFC) at 4 months and clinical follow up for up to 36 months. Sixty-one egg allergic children 5-17 years of age were randomized to egg-OIT (n=30) or egg avoidance (n=31) for 3 months. Egg avoidance was practiced for both groups after 3 months until 4 months, when DBPCFC was done for all. Those who passed the DBPCFC were advised to have egg as usual until 36 months follow up, throughout which immune markers and clinical events were studied. Among the egg-OIT group, 93% were desensitized after a median of 32.5 days, and 11/30 (37%) passed DBPCFC at 4 months, compared to 1/31 (3%) in the control group. These children were asked to have egg ad libitum, and adverse events were recorded 6 monthly up to 36 months post-OIT. Egg-OIT protocol has an initial fast escalation phase using dehydrated egg white (DEW) to a cumulative dose of 280mg in the first day, followed by a buildup phase towards a maintenance phase of eating at least one undercooked egg every 2 days. Adverse events from egg ingestion among those who passed the DBPCFC were mild and acceptable, and resolved without treatment. A significant decrease of Skin Prick Test (SPT) response to egg allergens was demonstrated in the OITG group at 4 months, so did the levels of specific IgE to egg allergens. A significant increase of egg white specific IgG4 was seen in the OTIG group after treatment.

This study has shown sustained results of desensitization of egg allergy. An egg-OIT regimen at a higher dosage of egg resulted in 37% success in passing DBPCFC 1 month post-treatment, without continued intake of egg, and the result was maintained up to 36 months afterwards. Another Italian study published this year has reported similar results, with 31% sustained tolerance 3 months after treatment[4]. This is good news to egg allergic patients as they will not have to continuously challenge themselves with egg in order to remain desensitized, while they will not be afraid of the occasional small or unknown amount of egg present in a normal diet. These reports should generate further studies to look at how OIT can be done to obtain the best sustained results without causing too much side effects and inconvenience. Important issues that require clarification through studies include: type and preparation of egg antigen, dosage and protocol to be used, duration of treatment and the monitoring of response. Answers to these uncertainties will hopefully bring about a wider application of OIT to egg and other foods.

References

1. Pratico AD et al. Immunotherapy: a new horizon for egg allergy? Expert Rev. Clin. Immunol. 10(5), 677–686 (2014).
2. Feldman MF, Bird JA. Oral immunotherapy for food allergy, ready for prime time? Heated egg and milk. Curr Allergy Asthma Rep. 2014; 14:436. DOI 10.1007/s11882-014-0436-6.
3. Escudero C et al. Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg allergic children. Clin Exp Allergy. 2015 Aug 3. doi: 10.1111/cea.12604.
4. Caminiti L et al. Oral Immunotherapy for Egg Allergy: A Double-Blind Placebo-Controlled Study, with Postdesensitization Follow-Up. J Allergy Clin Immunol Pract 2015;3:532-9.

International and local consensus on early peanut introduction and the prevention of peanut allergy in high-risk infants

Dr. Marco Hok-Kung Ho

MBBS, MRCP, MRCPCH, FHKCpaed, FHKAM
Specialist in Paediatric Immunology and Infectious Diseases
Consultant, Department of Paediatrics and Adolescence, Queen Mary Hospital

I am updating HKIA members on recent developments on early peanut introduction in infants as a result of the world's first LEAP study. This subject was reported in the last newsletter but it is a fast advancing field in Allergology.

A "Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants" has been published on 4 June by The Journal of Allergy and Clinical Immunology, an official journal of the American Academy of Allergy, Asthma & Immunology (AAAAI)[1].

This document was written by a panel of experts in consultation with the LEAP study investigators. They were representing American Academy of Asthma, Allergy, and Immunology; American Academy of Pediatrics; American College of Allergy, Asthma, and Immunology; Australasian Society of Clinical Immunology and Allergy; Canadian Society of Allergy and Clinical Immunology; European Academy of Allergy and Clinical Immunology; Israel Association of Allergy and Clinical Immunology; Japanese Society for Allergology, Society for Pediatric Dermatology; and World Allergy Organization.

The purpose was to highlight emerging evidence on the potential benefits of supporting early, rather than delayed, peanut introduction during the period of complementary food introduction in infants.

Interim guidance regarding early peanut introduction

1) There is now Level 1 evidence from a randomized controlled trial that healthcare providers should recommend introducing peanut-containing products into the diet of "high-risk" infants early on in life (between 4 – 11 months of age) in countries where peanut allergy is prevalent, since delaying the introduction of peanut may be associated with an increased risk of developing peanut allergy.
2) Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4-6 months of life, may benefit from evaluation by an allergist or physician trained in management of allergic diseases in this age group to diagnose any food allergy and assist in implementing these suggestions regarding the appropriateness of early peanut introduction.
3) LEAP trial suggested peanut ingestion of a median of 7.7 g peanut protein (interquartile range: 6.7 – 8.8 g)/week during the first 2 years. While the outcome of the LEAP regimen was excellent, the study did not address use of alternative doses of peanut protein; minimal length of treatment necessary to induce the tolerogenic effect; or potential risks of premature discontinuation or sporadic feeding of peanut.

HKIA has also issued a new local guideline based on LEAP trial recently[2].

Independently, it arrived at a very similar set of recommendations as its international counterpart. HKIA's local guideline is even more user-friendly. It not only shows a table informing us how to gauge peanut foods with approximately 6 grams of peanut protein, but also furnishes us with a management algorithm for easy reference.

The unresolved issues are: Firstly, both international and local guidelines have excluded patients with SPTs > 4 or 5 mm according to the current consensus. It is fairly unlikely that all of these patients would have failed a food challenge if they had been randomly assigned to early introduction. There can be debate as to a potential lost benefit in this population. Secondly, LEAP trial explored 5 years of consumption. The question remains as to how long peanut consumption would have to continue to confer benefit? A second phase of LEAP study called LEAP-ON will evaluate the persistence of tolerance to peanut, and whether continued consumption of peanuts is required to achieve tolerance, or if one can intermittently eat, or outright discontinue early introduction and remain tolerant? Thirdly, how critical is the definition of "high-risk" children and whether these findings may be relevant to children with lesser risk (e.g. milder eczema, cow's milk allergy not egg allergy, only positive family history) or no risk factors? Would a low prevalence region like HK benefit as much as the UK population? Further updates will follow on this immensely important area of allergy prevention when they become available. The results may have implications for other food allergies.

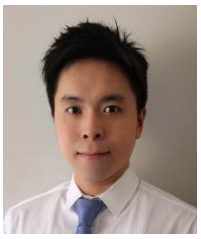
References

1. (AAAAI) David M. Fleischer, MD; (AAP) Scott Sicherer, MD; (ACAAI) 12 Matthew Greenhawt et al. www.jacionline.org/pb/assets/raw/Health%20Advance/journals/ymai/Consensus_Communication_Submission_Unmarked.pdf
2. June King-Chi Chan (Senior Dietitian, Allergy Centre, Hong Kong Sanatorium & Hospital), Alson WM Chan (Specialist in Paediatrics, Clinical Assistant Professor (Hon.), University of Hong Kong), Marco HK Ho (Consultant, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital), Tak-Hong Lee (Director, Allergy Centre, Hong Kong Sanatorium & Hospital).
   www.allergy.org.hk/HKIA%20-%20Guildelines%20for%20Prevention%20of%20Peanut%20Allergy%20(Final).pdf

New hopes for refractory atopic dermatitis: Victory in translational research

Dr. Johnny Chun-Yin Chan

MBBS(HK), MRCP(UK)
Specialist in Dermatology
Clinical Assistant Professor, Chief, Division of Dermatology
Department of Medicine, The University of Hong Kong



Background

Atopic dermatitis (AD) is a common, chronic, relapsing-remitting inflammatory skin condition on the background of allergy. AD affects 15 to 30% of children and 2 to 10% of adults in developed countries[1]. Clinically, AD is characterised by symmetric, erythematous patches or plaques with intense pruritus. Frequent scratching predisposes to secondary bacterial or viral infections. AD has imposed major burdens to the healthcare system and negative impacts on the quality of life on affected individuals. Significant psychosocial disturbances had been demonstrated among patients with AD in Hong Kong[2].

How far do we understand about the pathophysiology of atopic dermatitis?

Historically, there have been constant debates on the two major schools of thoughts concerning pathophysiology of AD. The 'outside-in' theory stresses on the importance of an epidermal-barrier defect as the starting event of AD, which leads to subsequent allergen-sensitisations and immunological events. On the other hand, the 'inside-out' theory suggest that AD is primarily due to an intrinsic immunological defect (skewed TH2 immunity), with epidermal dysfunction as a consequence. Despite the apparently exclusive nature of the two hypotheses, there has been increasing acceptance on the integrated role of the two in the pathophysiology of AD.

Recently, Noda *et al* published a comprehensive review on the immunological profile of AD, which summarised the key inflammatory mediators in the patho-mechanism of AD and highlighted the potential therapeutic targets[3]. It is now generally accepted that the over-expression of TH2 cytokines (IL-4, IL-5 and IL-13) and chemokines (CCL-17, CCL-18 and CCL-22), as well as the TH22 cytokine IL-22 are pivotal in the disease initiation and during early phase of AD. Important effects of these inflammatory cytokines include suppression of terminal differential proteins such as filaggrin (leading to the epidermal barrier function), inhibition of anti-microbial peptides (increased incidence of secondary infections), induction of epidermal hyperplasia (skin thickening) and potentiation of spongiosis (characteristic histopathological findings in AD) by the TH2 cytokines.

Existing treatments for AD and the unmet needs

Topical corticosteroid (TC) remains the mainstay of treatments in AD. Mild AD can usually be controlled by TC and topical calcineurin inhibitor. While for moderate and severe AD, systemic modalities are often required to attain significant disease control. Systemic therapies of AD include phototherapy (UVB / UVA) and immunosuppressive agents including azathioprine, mycophenolate mofetil, cyclosporine and methotrexate. Phototherapy is efficacious in improving AD and safe in general, but the application is limited by the availability of facilities and time constraints. In practice, oral immunosuppressants are effective in around two-third of patients with moderate-to-severe AD (by definition with more than 50% improvement in objective assessment of AD in terms of erythema, induration and scaling). Systemic immunosuppressants target on the 'up-stream' immune system and act by non-specific inhibition of T-cells and or B-cells. Infective complications are the main concerns due to profound immunosuppression. Patients will also need to be monitored on the liver and renal functions, based on the side effect profile of individual immunosuppressant. In addition, a significant proportion of patients (20-30%) experience suboptimal response to systemic immunosuppressants and even combination therapies. There is an immense need for development of new therapies for recalcitrant AD and perhaps to replace the existing non-specific, potent immunosuppressants.

The new paradigm in the treatment of AD

With better understandings of the pathophysiology in AD, therapeutic agents that target the specific key inflammatory mediators related to AD are being developed. Efforts had been made to tackle the robust TH2-mediated immune response in AD. The TH2 cytokines IL-4 and IL-13 are widely-accepted to have played significant roles in the pathogenesis of AD. Recently, dupilumab, a fully human monoclonal antibody, targeting the alpha subunit of IL-4 receptors and blocking downstream signalling from both IL-4

and IL-13, had been evaluated on the clinical efficacy and safety in treating patients with moderate-to-severe AD. Dupilumab is not a new candidate in the field of allergy. It had previously been showed to be effective in improving moderate-to-severe asthma[4].

Dupilumab treatment in adults with moderate-to-severe atopic dermatitis

Beck *et al* had conducted four separate multi-national (involving the United States and Europe), randomised, double-blinded, placebo-controlled trials on dupilumab in subjects with moderate and severe AD[5]. Dupilumab was evaluated as monotherapy in two independent 4-week trials, one 12-week trial and as combination therapy with topical corticosteroid in one 4-week study. Clinical endpoints including the Eczema Area and Severity Index (EASI) score, investigator's global assessment score (IGA), degree of severity of pruritus, side effect profile and level of biochemical markers (i.e. thymus and activation-regulated chemokine [TARC] and IgE) were investigated in all studies.

Similar encouraging results were obtained in the two 4-week trials with dupilumab as monotherapy. Subcutaneous injection of dupilumab was associated with rapid (statistically significant effects notable within two weeks of administration) and dose-dependent improvement (300mg/wk > 150mg/wk > 75mg/wk) in all clinical endpoints and significant reduction in the serological levels of TARC and IgE. In the 12-week trial, continuation of dupilumab treatment had resulted in further improvement clinically (85% of subjects was able to achieve 50% reduction in EASI score and 56% of pruritus by 12 weeks). In the 4-week trial of combination therapy of dupilumab and topical corticosteroid, all subjects receiving the combination therapy achieved 50% reduction in the EASI score by the end of study in 4 weeks as compared to only 50% among subjects receiving combination therapy with topical corticosteroid and placebo.

Favorable safety profiles were observed in all four clinical studies. Adverse events were reported at a similar frequency among subjects receiving dupilumab and placebo. Most adverse effects were mild and transient in nature. Nasopharyngitis, headache and injection-site reactions were more frequently observed in the dupilumab groups and were all self-limiting.

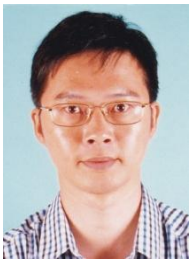
Clinical implications to Hong Kong

In November 2014, the United States Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to dupilumab for the treatment of adults with moderate-to-severe atopic dermatitis (AD) who are not adequately controlled with topical prescription therapy and/or for whom these treatments are not appropriate. The research findings for dupilumab have been transformational, however, the study data were based on Caucasian subjects so far. Data on the clinical efficacy among Asian patients and the long term safety are much in need before commencement of dupilumab as the standard treatment in AD. To address the issue, a large-scale, multi-centered trial has been kicked off in several Asian countries including Hong Kong since early 2015. The first-phase double-blinded, randomised, placebo-controlled study is towards the end of a 24-week study period in Queen Mary Hospital. The drug is anticipated to be registered in Hong Kong within the next two years and hopefully can bring about new hope for local patients with refractory AD.

References

1. Williams H et al. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. J Allergy Clin Immunol 2006; 118:209-213.
2. Hon KL et al. Does age or gender influence quality of life in children with atopic dermatitis? Clin Exp Dermatol 2008; 33(6):705-9.
3. Noda S et al. The translational revolution and use of biologics in patients with inflammatory skin diseases. J Allergy Clin Immunol 2015; 135:324–336.
4. Wenzel S et al. Dupilumab in Persistent Asthma with Elevated Eosinophil Levels. N Engl J Med 2013; 368:2455-66.
5. Beck LA et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014; 371[2]:130-9.

Celiac disease



Dr. Eric Yuk-Tat Chan

MBBS, FRCPath, FRCPA, FHKCPath, FHKAM
Consultant, Division of Clinical Immunology, Department of Pathology and Clinical Biochemistry
Queen Mary Hospital

Celiac disease (CD) is an immune-mediated disorder occurring in genetically susceptible individuals. It is initiated by dietary gluten which is activated by the enzyme tissue transglutaminase (tTG); then presented to T-helper cells in the gut, resulting in release of cytokines that cause the characteristic clinical and histological features of the disease. A full review article was published recently in the Journal of Allergy and Clinical Immunology[1].

The prevalence of CD is around 1% in Western countries but this figure is thought to be a gross under-estimate. Moreover the incidence is rising due to an increased awareness of the disease and a true increase. CD is reported to be rare in the Far East and the Sub-Saharan Africa. In Hong Kong, although the diagnostic serological tests of CD have been available for more than 10 years, to the author's knowledge, a definite case of CD is yet to be identified. It is not known whether the occasional positive antibody results signify potential CD, defined as positive CD serology with normal biopsy, or represent false positives.

In CD, HLA-DQ2 occurs in 95% and HLA-DQ8 in 5-10% of patients. HLA-DQ2 becomes the second highest risk factor for CD, after having a positive family history. The rarity of CD in Chinese may be explained by (i) the lower frequencies of HLA-DQ2 and HLA-DQ8 in Chinese which were 18.4% and 8.0% respectively[2], compared to 30-35% of the Caucasian population carrying these markers; (ii) the lower consumption of wheat in the past; (iii) other environmental factors.

Of the various autoantibody tests that are available for the diagnosis of CD, anti-tissue transglutaminase (tTG) has the highest sensitivity and specificity and this is the only test currently available locally. It is a quantitative assay and the result can also be used to monitor adherence to gluten-free diet. Other autoantibodies such as anti-endomysium, anti-deamidated gliadin peptide, anti-gliadin are of supplementary role only. The isotype of these autoantibodies is IgA and total IgA should also be measured to exclude IgA deficiency which is more common in patients with CD. In these cases the IgG isotype of these autoantibodies can be measured. According to the new guidelines from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN 2012)[3] for a symptomatic child with high IgA anti-tTG a diagnosis can be made if additional blood tests are positive, thus avoiding duodenal biopsy. Additional blood tests include a further high IgA anti-tTG result, positive anti-endomysium and positive HLA-DQ2/8 haplotype.

References

1. Peter H.R. Green *et al*. Celiac disease. Journal of Allergy and Clinical Immunology 2015; 135: 1099–1106.
2. Yuan J *et al.* The tip of the "celiac iceberg" in China: a systematic review and meta-analysis. PLoS One. 2013; 8(12):e81151.
3. Husby S *et al*. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012; 54(1):136-60. [Erratum in J Pediatr Gastroenterol Nutr. 2012; 54(4):572].

Incidence and features of systemic reaction to skin prick test

Ms. Maggie Pik-Kee Lit

Bachelor of Nursing (BN), Master of Nursing (MN), Board of registered Polysomnographic Technologists (RPSGT)
Fellow of Provisional Hong Kong Academy of Nursing in the specialty of Medicine-Respiratory Advanced Practice Nurse

Sellaturay P[1] reported an incidence rate of 0.07% of systemic reactions after skin prick tests (SPT) in a largest single-centre study from a teaching hospital at Cambridge of the United Kingdom. Twenty-four patients (mean age 23.5 years) was identified to suffer from systemic reactions in the 6-year (2007-2013) retrospective study. More than half were mild cutaneous reactions only, though airway involvement or hypotension were also observed. The study also reported the second case of systemic reaction to a drug (Tazocin), which was a severe one with wheeze, dyspnea and tachycardia. The patient was treated with epinephrine, nebulized bronchodilators, corticosteroid and anti-histamine. Food was reported to be the commonest cause (75%) of reactions and nuts were found to be the culprits in more than half. The other observed possible associations with systemic reactions to SPT include asthma, severe initial reaction or allergic disease before SPT and a large SPT wheal.

SPT is a commonly practiced test in the management of allergic diseases and has all along been considered a safe test. According to this group of authors, no fatalities had been recognized in the medical literature in the past 14 years. Reports in the 1980s to 1990s[2-4] also revealed rare occurrences of fatalities in association with SPT (in contrast to intradermal testing). However, the significance of systemic reactions, particularly with food allergens, is not to be neglected and had been reported in the recent literature. As a result, SPT, being tests not without risks, should be performed in a setting with adequate resuscitative equipment and treatment, and by staff with adequate training to handle such possible reactions. Such precautions had also been spelled out in a recent review[5]. In addition, extra caution would also be exercised when SPT is being performed during the respective season when the patient has allergic symptoms.

References

1. Sellaturay P, Nasser S and Ewan P. The incidence and features of systemic reactions to skin prick tests. Ann Alergy Asthma Immunol 2015 Aug 5 pii:S1081-1206(15)00450-0. [Epub ahead of print]
2. Lockey RF, Bebedict LM, Turkeltaub PC, et al. Fatalities from immunotherapy and skin testing. J Allergy Clin Immunol 1987; 79:660-677.
3. Redi MJ, Lockey RF, Turkeltaub PC, et al. Survey of fatalities from skin testing and immunotherapy 1985-1989. J Allergy Clin Immunol 1993; 92: 6-15.
4. Bernstein DI, Wanner MM, Borish L, et al. Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. J Allergy Clin Immunol 2004; 113: 11229-1136.
5. Heinzerling L, Mari A, Bergmann K-C, et al. The skin prick test-European Standards. Clinical and Translational Allergy 2013; 3:3.

Progress report on Hong Kong Institute of Allergy

Dr. Tak-Hong Lee

CBE, MD, ScD, FRCP, FRCPath, FHKCP
Specialist in Immunology and Allergy
President, Hong Kong Institute of Allergy

Time flies and it's been 9 months since I became President so I thought I would provide an update on progress. My six-monthly report was already loaded on to our webpage (www.allergy.org.hk/president.html).

As always I thank the officers and colleagues on Council without whose wisdom and support nothing could have been achieved. I also thank Ms. Sigourney Liu and her team at MIMS who have performed the duties of our secretariat with patience and efficiency.

At the Think Tank meeting at the start of my term, Council agreed unanimously to shape a strong professional platform for the benefits of allergic patients in Hong Kong in the following ways:

- *Increase allergies' public and professional profile;*
- *Create more opportunities for training of aspiring allergists and allied health professionals;*
- *Promote an environment to facilitate discovery of new knowledge;*
- *Progress an agenda to help improve allergy services.*

I am pleased to report that significant progress has been made in many areas as detailed below.

We are very honoured that Dr. Ko Wing-man, BBS JP, Secretary for Food and Health in the Government of the Hong Kong SAR has accepted our invitation to become HKIA's new Patron. We invited him to an informal dinner at the Hong Kong Club to meet members of Council and key individuals who help us in the administration of our Institute.

A number of new subcommittees were established to drive forward our agenda:

1) *Scientific Programme and Research (co-chair: Prof. Ting-Fan Leung and Prof. Gary Wong)*
2) *Public Engagement (co-chair: Dr. Henry Chan and Dr. Marco Ho)*
3) *Publication (chair: Dr. Jane Chan)*
4) *Social Programme (chair: Dr. Robert Tseng)*
5) *Membership (co-chair: Dr. Johnny Chan and Dr. Kit-Man Sin)*
6) *Education, Training and Fellowships (co-chair: Dr. Fanny Ko and Dr. Adrian Wu)*
7) *Immunology (co-chair: Dr. Eric Chan and Dr. Roland Leung)*
8) *Service Development (co-chair: Dr. Tak-Hong Lee and Dr. Christopher Lai)*
9) *Allied Health Professionals and Health Promotion (co-chair: Ms. June Chan and Ms. Maggie Lit)*
10) *Finance (co-chair: Dr. Alice Ho and Dr. Tak-Fu Tse)*

The highlights of each subcommittee's work are summarized below:

1) *<u>Scientific Programme and Research</u>*
   - An evening symposium on "Allergy Prevention and Management in 2015 and Beyond" sponsored by Danone Nutricia was held on 4 December 2014 at the Mira Hotel. 185 registrations were received. The overall turn up rate was 75%;
   - A pilot research grant proposal scheme has been approved by Council;
   - 9th HKIA International Allergy Convention will be held on 8 – 9 October 2016 at the Hong Kong Convention and Exhibition Centre and the Organising Committee (Chaired by Prof. Gary Wong) is starting to design an exciting scientific programme. Invitations have been sent to several other Allergy Societies internationally to join with HKIA to co-organise the event. The British Society of Allergy and Clinical Immunology (BSACI) has already accepted and the European Academy of Allergy and Clinical Immunology (EAACI) has also indicated a strong interest to participate by sending some speakers. This will be a special Convention as HKIA will be celebrating its 20th birthday;
   - On 17 September 2015, HKIA and the Hong Kong Society for Paediatric Immunology Allergy and Infectious Diseases hosted a successful dinner symposium on "Allergy Prevention Begins At Your Practice" at the Mira Hotel sponsored by Danone Nutricia. There were around 200 attendees. Please see later in newsletter for more details.

2) *Public Engagement*
- A press conference on "Allergy Risk in Infants and Young Children Survey Results" co-organized by the Hong Kong Allergy Association and HKIA was held on 28 April 2015;
- There will be more collaborations between HKIA and the Hong Kong Allergy Association in the future so that we can speak with one voice in the public domain;
- HKIA with other colleagues are helping the Environmental Protection Department of the Government of HKSAR to produce a series of short educational video clips to be aired widely on TV within a few months to engage the public about pollution and its health hazards.

3) *Publication*
- First issue of our e-newsletter had been published and sent to members on 15 April 2015. The second one will be published in October, at which time there will be a once off mailing of both 2015 e-newsletters by MIMS to an extensive database of doctors and others to broaden the readership. We will take the opportunity in the mailing to invite readers to subscribe to the free six monthly e-newsletters by joining HKIA;
- Consultations on "Guidelines for the Diagnosis and Management of Cow's Milk Protein Allergy (CMPA) in Hong Kong" and "Guidelines on Prevention of Peanut Allergy" were completed. Both guidelines have already been uploaded onto HKIA's website (http://www.allergy.org.hk/);
- HKIA position paper on "Guidelines for Allergy Prevention in Hong Kong" has just finished its consultation. The final approved version will be uploaded onto the website shortly.

4) *Social Programme*
- A BBQ dinner for members and families will be held at the HK Golf Club in November 2015.

5) *Membership*
- Number of members increased from 401 in December 2014 to 495 in September 2015. We are targeting a doubling in membership numbers in the first three years of my Presidency;
- Joining fee and annual subscription fee waived for two years, so this is a great time to join. Benefits of membership include substantial discounts to attend conferences and workshops hosted by HKIA. Council will identify sponsors for applicants who do not know of another member;
- Schemes to offer HKIA scholarships for travel to conferences and training grants for studying overseas have been approved by Council. Details are being finalized;
- HKIA will sponsor Dr. Gilbert Chua to attend the 24th World Allergy Congress to be held on 14 – 17 October 2015 in Seoul, Korea. He will represent HKIA to look after its booth.

6) *Education, Training and Fellowships*
- A certificate course on "Diagnosis and Management of Allergy" co-organized with the Federation of Medical Societies of Hong Kong will be held on 6 October to 10 November 2015 (every Tuesday). 110 registrations have been received and it is fully subscribed.

7) *Immunology*
- HKIA will be co-organizing clinical laboratory allergy meetings with the Department of Pathology of Queen Mary Hospital (QMH) twice a year. This will be a 1.5 hours programme on a different theme each time. The first meeting was held on 29 September 2015 on Aneasthetic drug allergy (please see summary later in newsletter). Members are encouraged to support and attend these excellent educational opportunities. More details will follow.

8) *Service Development*
- A "bottom up" strategy will be adopted to increase educational initiatives and start to grow allergy expertise from interested clinicians and allied health professionals;
- It is hoped that an Allergy Board will set up at QMH and allergy case presentations will be organized every 6 weeks alternatively at QMH and Hong Kong Sanatorium and Hospital. Council will reassess at a later stage the need for HKIA to establish its own independent clinical workshops;
- QMH/HKU has been awarded a new Resident post that will specialise in Allergy and Immunology. Part of his training will be undertaken at the Allergy Centre, Hong Kong Sanatorium and Hospital.

9) *Allied Health Professionals and Health Promotion*
- Allergy-related talks will be delivered to allied health and nursing professionals twice a year in January and June starting in January 2016. Details will follow.

10) *Finance*
- The financial situation of the Institute remains healthy. HKIA has secured several major unrestricted educational grants; Danone Nutricia, Nestle (Hong Kong) Ltd., A.Menarini, AstraZeneca and Mundipharma have become our major corporate sponsors.

I thank our membership, which is growing weekly, for its continuing support. Long may it continue! Please don't hesitate to contact me if you have any comments or suggestions. I would like to hear from you.

Highlights of the Allergy Prevention Symposium

Dr. Alson Wai-Ming Chan

MBChB, DCH (Ireland), Dip Ger Med RCPS (Glasg), PdipCommunityGeriatrics (HK), MRCPCH, FHKCPaed, FHKAM(Paed)
Specialist in Paediatrics

A scientific symposium was held on 17 September 2015 to launch the HKIA Guidelines for Allergy Prevention in Hong Kong, co-hosted by the Hong Kong Institute of Allergy and the Hong Kong Society for Paediatric Immunology, Allergy and Infectious Diseases.

Professor Ting-Fan Leung highlighted that allergic diseases are common in the economically developed countries. Among children and adolescents in Hong Kong, 40% of school age children have allergic rhinitis, 15% and 10% of secondary school children have eczema and asthma respectively, and 5-10% of preschool children have adverse food reactions. Shellfish and eggs are the most common food allergens in our locality.

Then Dr. Alfred Yat-Cheung Tam discussed the environmental influences on allergy. In particular, traffic air pollution and exposure to tobacco smoke are associated with increased allergic diseases including asthma, allergic rhinitis, eczema and allergic sensitization. Exposure to house dust mite, damp home environment, mold inside the house, use of foam pillow, and exposure to gas cooking fuel are all associated with asthma or recurrent wheeze. Besides, early viral infections, especially Respiratory Syncytial Virus (RSV) and Human Rhinovirus (HRV) are found to be associated with increased asthma and wheeze in later life.

Dr. Alson Wai-Ming Chan then elaborated on the dietary and lifestyle influences on allergy. A healthy diet without restriction is recommended for mothers during pregnancy and lactation. Breastfeeding is the best nutrition for infants in the first 6 months. Introduction of complementary food should start from 4-6 months. Recent research studies are suggesting that food allergen avoidance during pregnancy and early infancy were associated with increased risk of allergies.

Finally, for lifestyle influences, the Body Mass Index (BMI) shows a clear positive dose-response relationship with asthma, and the association with eczema is also significant. Adverse psychosocial events during pregnancy and early childhood are associated with increased risk of allergy.

In conclusion, strengthening of immune tolerance is the current focus on allergy prevention. The greater the exposure to environmental and commensal microbes in terms of diversity and quantity during infancy and early childhood, the greater is the development of immune tolerance and lesser the atopic tendency. A summary of allergy prevention measures are summarized in the following table:

Allergy Prevention Measures

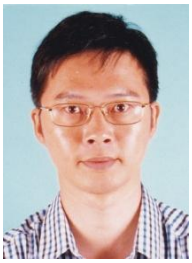
1.	No unnecessary diet restriction during pregnancy and lactation
2.	Breastfeeding in the first 6 months of life
3.	Consider hydrolyzed formula milk if exclusive breastfeeding is not feasible in high risk infants
4.	Introduce complementary food from 4-6 months of age when developmentally ready
5.	Control air pollution
6.	Avoid smoking, both active or passive smoking
7.	Control indoor air quality
8.	Weight control and avoid obesity
9.	Avoid excessive psychological stress
10.	Immunization as recommended
11.	Judicious use of antibiotics
12.	Early treatment and control of atopic diseases

A full version of the Guidelines for Allergy Prevention in Hong Kong can be found on the Hong Kong Institute of Allergy website: www.allergy.org.hk/approved_guidelines.html

Allergy Prevention Symposium, jointly hosted with HKSPIAID, gained impressive traction with 49% MORE attendance than previous seminar held in December 2014.

Institute	Specialty	Total Registration	Attendance (% show up)
Private and Public Hospitals	Registered Nurse	51	45 (88%)
Medical Societies	PD + OG + GP	91	60 (66%)
Hong Kong Dietitian Association + Hong Kong Nutrition Association	Dietitian + Nutritionist	90	95 (105%)
	Grand Total	232	200 (86%)

Report on the recent Clinical Laboratory Allergy Meeting on Anaesthetic Drug Allergy jointly held by Queen Mary Hospital and the Hong Kong Institute of Allergy



Dr. Eric Yuk-Tat Chan

MBBS, FRCPath, FRCPA, FHKCPath, FHKAM
Consultant, Division of Clinical Immunology, Department of Pathology and Clinical Biochemistry
Queen Mary Hospital

Summary

In early 2015, following the success of the Division of Clinical Immunology, Department of Pathology and Clinical Biochemistry at Queen Mary Hospital (QMH) in holding regular clinical meetings on Neuro-immunology,in liaison with territory-wide neurologists, the Division decided to explore similar clinical meetings in conjunction with the Hong Kong Institute of Allergy (HKIA) to further develop the shared interest in Clinical Laboratory Allergy. The new clinical meeting is planned to be held every 6 months on selected allergy topics. Medical doctors and other healthcare professionals interested in clinical and laboratory aspects of allergy are all welcome to attend.

The very first clinical meeting on Clinical Laboratory Allergy jointly held by QMH and the HKIA was launched at QMH on 29 September 2015. Professor Tak-Hong Lee, the HKIA President, chaired this meeting. The theme was Anaesthetic Drug Allergy, a topic close to the heart of anaesthetists as well as allergists. Details of speakers and their topics can be found in the earlier announcement as shown below. Participants included anaesthetists, physicians, paediatricians, pathologists and laboratory workers. In this meeting the clinical and laboratory aspects of the anaesthetic drug allergy were reviewed and clinical cases were presented as illustrations. The meeting was well attended by 50-60 participants, half of whom were from Anesthesiology.

Kindly see our earlier announcement as shown below:

瑪麗醫院 QUEEN MARY HOSPITAL

Department of Pathology & Clinical Biochemistry

Hong Kong Institute of Allergy

Clinical Laboratory Allergy Meeting

Date: 29 September 2015 (Tuesday)
Time: 6:00 pm – 7:30 pm
Theme: Anaesthetic Drug Allergy
Chairman: Professor Lee Tak Hong
Venue: Room 004, University Pathology Building, Queen Mary Hospital

Program	Speaker
Introduction	Professor Lee Tak Hong, President, Hong Kong Institute of Allergy
Clinical and laboratory investigations of anesthetic drug allergy (20 min)	Dr. Kwok Wing Hong, Consultant, Department of Anesthesia & Intensive Care, PWH Dr. Eric Chan, Consultant, Department of Pathology and Clinical Biochemistry, QMH
Clinical experience in QMH – case sharing (40 min)	Dr. Marco Ho, Consultant, Department of Paediatrics and Adolescent Medicine, QMH Dr. Elaine Au, Resident, Department of Pathology and Clinical Biochemistry, QMH
Clinical experience in PWH – case sharing (30 min)	Dr. Kwok Wing Hong, Consultant, Department of Anesthesia & Intensive Care, PWH

BBQ Evening on 3 October 2015

Congenial social interactions have always been an important feature of HKIA. These parties have normally been in the context of conferences. While this tradition will continue, it seems opportune to have more get togethers for members to meet informally as our membership grows.

Therefore Dr. Robert Tseng and Dr. Gilbert Chua arranged a poolside Asian BBQ buffet at the lovely HK Golf Club, Deep Water Bay, on 3 October 2015 courtesy of the kindness of Dr. Tse Tak-Fu and Dr. Helen Chan. The evening was subsidised by HKIA.

Unfortunately the weather did not cooperate and typhoon signal 3 was hoisted. Intermittently there were sleeting rain and winds, so the BBQ was postponed. The event will be rescheduled so please watch this space.

More than 30 people registered for this first event including children of members. This was great news and a start. It is hoped that more members and their families may like to join in future festivities and meet other members.

Certificate Course on Diagnosis and Management of Allergy, 6 October – 10 November 2015

Announcement

Certificate Course on Diagnosis and Management of Allergy will be commenced on 6 October 2015. 110 free registrations were filled up. We would like to take this opportunity to thanks all speakers, AstraZeneca Hong Kong Limited's support and the continuous support from the members.

The 9th Hong Kong Allergy Convention 2016, 8 – 9 October 2016

Announcement

Allergic diseases are fast becoming one of the most prevalent health problems in the world. We cordially invite you to participate in the Hong Kong Allergy Convention on 8 - 9 October 2016 at the Hong Kong Convention and Exhibition Centre. The theme of the Convention is ***"Novel Strategies for Prevention and Treatment of Allergic Disorders"***.

The forthcoming Convention will be the ninth time that the Hong Kong Institute of Allergy (HKIA) and the American College of Allergy, Asthma and Immunology (ACAAI) have joined hands in organizing an international conference in Hong Kong. We are delighted on this occasion to have the British Society for Allergy and Clinical Immunology (BSACI) to support our 2016 Convention too.

The Convention has been one of the most important learning and networking platforms for medical professionals in the region. Graced by contributions from numerous world authorities in allergies, the Convention will be a superb occasion to be updated on novel strategies for prevention and treatment of allergic disorders.

We look forward to seeing you at the HKAC 2016!

Meetings

Overseas Meetings

World Allergy Congress (WAO)
14 - 17 October 2015 / Seoul, Korea (www.worldallergy.org.wac2015)

American College of Allergy, Asthma and Immunology (ACAAI)
5 - 9 November 2015 / San Antonio, Texas, USA (www.acaai.org)

Australian Society for Immunology (ASI)
29 November - 3 December 2015 / Canberra, Australia (www.immunology.org.au)

Winter Meeting of British Thoracic Society (BTS)
2 - 4 December 2015 / London, United Kingdom (www.brit-thoracic.org.uk)

American Academy of Allergy Asthma and Immunology (AAAAI)
4 - 7 March 2016 / Los Angeles, USA (www.aaaai.org)

American Thoracic Society (ATS)
13 - 18 May 2016 / San Francisco, California (www.thoracic.org)

European Academy of Allergy and Clinical Immunology (EAACI)
11 - 15 June 2016 / Vienna, Austria (www.eaaci2016.org)

65th Meeting of Japanese Society of Allergology (JSA)
17 - 19 June 2016 / Tokyo, Japan (www.jsaweb.jp)

European Respiratory Society (ERS)
3 - 7 September 2016 / London (www.ersnet.org)

Local Meetings

Certificate Course on Diagnosis and Management of Allergy (HKIA)
6 October - 10 November 2015 (every Tuesday) (www.allergy.org.hk)

Autumn Respiratory Seminar of Hong Kong Thoracic Society (HKTS) and CHEST (Delegation HK & Macau)
14 - 15 November 2015 (www.hkresp.com)

Annual Scientific Meeting of Hong Kong Thoracic Society (HKTS) and CHEST (Delegation HK & Macau)
20 March 2016 (www.hkresp.com)

9th Hong Kong Allergy Convention (HKIA)
8 – 9 October 2016 (www.allergy.org.hk/hkac2016.html)

Gold Sponsor

DANONE NUTRICIA
Early Life Nutrition

Silver Sponsor

Nestlé
Start Healthy
Stay Healthy

Other Corporate Sponsors

AstraZeneca
阿斯利康

mundipharma