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Dr. Jaime S. ROSA DUQUE

MD (UCI, USA), PhD in Pharmacology and Toxicology (UCI, USA), LMCHK (UCI, USA), DCH (UK), FHKCPaed, FHKAM (Paediatrics), Diplomate of the American Board of Pediatrics, FAAP, Diplomate of the American Board of Allergy and Immunology, FACAAI, FAAAAI
Clinical Assistant Professor (Practice), Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong

I hope things have been improving for most of you, with at least the local COVID-19 infection rate under better control this year as more people are getting vaccinated. The vaccination program has helped provide immunity protection for many of us and members of our community. With this improving situation and particularly many thanks to the outstanding work by the Organizing Committee, HKIA recently held a very successful and educational HK Allergy Convention. The Convention was filled with incredible speakers and topics, followed by a get-together dinner consisting of the HKIA group. The event in its entirety was beautiful!

Here, I first thank Dr. Temy Mok for her 3 years of service as Associate Editor. Her helpful ideas and efforts played an immense role in elevating the HKIA e-Newsletter in its current form. At the same time, it is also my pleasure to welcome Dr. Allie Lee, Assistant Professor of the Department of Ophthalmology at the University of Hong Kong, as the Editorial Team's new Associate Editor. She will also continue to lead as one of the subeditors of the newly launched section, Eye Allergy.

In reflecting these changes, I have also just come to realize that I have already just served 3 years as the Chief Editor. Time flies when one is having fun! During this time, the topic categories had expanded, such as the sections Allied Health Professional and then Eye Allergy. On occasion, we even had industry scientists, allergy patients and doctors from the HK Infection Disease Centre share their experiences with us. A huge applause to Dr. Temy Mok, Dr. Agnes Leung and Dr. Jason Chan for their important contribution to the HKIA e-Newsletter as Issue Editors during the expansion from one to three Associated Editors. There is also now a more electronic friendly system, with HTML web-based Table of Contents emailed to all of you and cross referencing to the original article and PubMed websites. The visual of the articles have also been enhanced due to your creativity in formulating tables, figures and other illustrations. For the future, it is my thought that for the best of HKIA e-Newsletter, an adjustment of the leadership of the Editorial Board could be beneficial in achieving potentially other constructive, bright ideas. I do have someone outstanding in mind to suggest, which shall be revealed soon…

Again, huge thanks to all of you so that the HKIA e-Newsletter once again is able to come up with the following useful yet concise articles. As this pandemic continues, some will include topics related to COVID-19, while others continue to update us about the bread-and-butter allergy practice. Enjoy!

Dr. Jaime Sou Da Rosa Duque
Editor, HKIA e-newsletter
The Hong Kong Institute of Allergy

Asthma and osteoporosis

Dr. Veronica L. CHAN

MBChB, MRCP (UK), FRCP (Edinburgh), FHKAM
Specialist in Respiratory Medicine
Head of TWGHs Medical Centre (North Point)
Medical Division, Tung Wah Group of Hospitals

Introduction

The Global Initiative for Asthma (GINA) guidelines now suggest that all adults and adolescents with asthma should receive inhaled corticosteroid (ICS) treatment to reduce the risk of serious exacerbations.[1] The ICS can be delivered in a stepwise approach, by as-needed low-dose ICS-formoterol as in mild asthma, or by regular daily controller as in moderate to severe asthma. Short course of oral corticosteroids (OCS) could be used for patients experiencing severe asthma exacerbations. Both ICS and OCS are known to have deleterious side effects. One of the long-term adverse effects is osteoporosis which can lead to fragility fracture with subsequent increased health care costs, morbidity and mortality.[2]

Osteoporosis is a systemic bone disorder characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue, which leads to reduced mechanical strength and an increased risk of fracture. BMD is measured by dual-energy X-ray absorptiometry (DEXA) scan and is expressed as a T-score, which reflects the number of standard deviations (SDs) the measured BMD differs from BMD in healthy young individuals. Osteoporosis is defined as low energy fracture in the spine or hip or a BMD T-score ≤ −2.5 at the lumbar spine or hip region.[3]

Well-known risk factors for osteoporosis include smoking, female sex, advanced age, low body weight, early menopause, malnutrition, and genetic susceptibility. Some of these risk factors are common for both osteoporosis and asthma. Patients with asthma tend to have additional risk factors for osteoporosis, including systemic inflammation, vitamin D deficiency, and sedentary life style.[4] Long-term use of corticosteroids has been associated with increased risk for osteoporosis and fracture. Systemic corticosteroids increase renal excretion of calcium and decrease intestinal calcium absorption, which leads to a negative calcium balance and activation of osteoclasts and bone resorption. Furthermore, corticosteroids decrease osteoblastogenesis and bone formation. Glucocorticoid-induced bone loss is more marked at skeletal sites with a high trabecular content, and is more rapid in the first 12-24 months of treatment. Fracture risk increases markedly within 3 to 6 months after initiation of systemic corticosteroid therapy ≥ 5 mg of prednisolone (or equivalent) daily. The intermittent use of short course of OCS in patients with asthma for acute exacerbation have less deleterious effects with regard to bone loss, but maximum tolerable amount of OCS given as separate short courses is unclear and probably unique to each individual. The effect of long-term use of ICS on BMD and risk of osteoporotic fracture is controversial. Two recent studies have attempted to address this issue.

Association of asthma with osteopenia, osteoporosis, osteomalacia, and fractures[5]

Data from the 2006-2012 Nationwide Emergency Department Samples in the United States were used to search for a primary and/or secondary diagnosis of asthma, and the dependent variables of osteoporosis, osteopenia, osteomalacia, and specific type of fractures. There were 198,102,435 children and adults including 10,129,307 with asthma, which accounted for an approximately 20% sample of emergency department (ED) visits throughout the United States of America. In a pooled analyses of data from all 7 years, asthma versus no asthma was associated with higher odds of osteoporosis (adjusted odds ratio [aOR] 1.85 [95% confidence interval {CI}, 1.82-1.88]), osteopenia (aOR 1.45 [95% CI, 1.41-1.50]), osteomalacia (aOR 2.00 [95% CI, 1.61-2.49]), and pathological fractures (OR 1.24 [95% CI, 1.20-1.27]).

Risk of osteoporosis and fragility fractures in asthma due to oral and inhaled corticosteroids: two population-based nested case-control studies[6]

Two population-based nested case-control studies were conducted to evaluate the risk of osteoporosis and fragility fractures in people age >18 years taking ICS and OCS for asthma. They utilized data from the Clinical Practical Research Datalink and Hospital Episode Statistics in July 2018. This dataset covered more than 15.4 million patients from 738 practices across the United Kingdom, equivalent to approximately 7% of the population. Among all adult patients with asthma, they identified cases of osteoporosis and fragility fracture (a composite of vertebral, hip, forearm-wrist and humeral fractures), and matched each case with randomly selected patients with asthma by age, gender and practice. A dose-response relationship was observed between the number of prescriptions and cumulative dose of corticosteroid in the year prior and risk of osteoporosis or fragility fracture. Comparing with no use of corticosteroids, even two or three OCS prescriptions, or one to six ICS prescriptions in the previous year increased the risk of osteoporosis ([aOR 1.34, 95% CI, 1.12 to 1.66] and [aOR 1.35, 95CI, 1.14 to 1.59] respectively). The effect size of corticosteroids on fragility fracture was smaller than on osteoporosis. Having more than 3 prescriptions of OCS or more than 6 prescriptions of ICS was associated with increased risk of fragility fracture ([aOR 1.31, 95% CI, 1.12 to 1.77] and [aOR 1.24, 95% CI, 1.01 to 1.53] respectively). Higher cumulative doses and number of OCS and ICS prescriptions were associated with increased odd of osteoporosis and fragility fracture, with a clear dose-

response relationship.

Assessment for risks of osteoporosis

The latest GINA guideline[1] recommends use of ICS in all patients with asthma, even for those with mild and intermittent symptoms. This will definitely increase use of ICS. Although the GINA report highlights the risks of osteoporosis and fractures associated with these treatments, they do not cover the preventive strategies in detail. Physicians should have a high index of suspicion, especially if there are other co-existing risk factors for osteoporosis, as shown in table 1.[7] Bone mineral density (BMD) testing by DEXA scan is recommended for people who receive glucocorticoids and are at least 40 years of age.[2] The fracture risk assessment tool (FRAX) (https://www.sheffield.ac.uk/FRAX/) can also be used, which combines many risk factors for osteoporosis (including glucocorticoid use) with the bone mineral density to provide an estimate of the 10-year risk of major osteoporotic fracture and hip fracture among patients who are at least 40 years of age.[8]

Prevention and treatment for osteoporosis[2,7]

Asthma management should be optimized, with strategies to maintain good symptom control, reduce the risk of asthma exacerbations, and minimize the need for OCS. The use of ICS should be kept to the minimum necessary to treat symptoms and should be stepped down if symptoms and exacerbations are well managed. Routine life-style recommendations should be implemented, including smoking cessation, limitation of alcohol consumption, maintenance of normal weight, weight-bearing exercise, and fall prevention. Adequate dietary intake of calcium (1000mg per day) and vitamin D (600-800IU) is encouraged in patients who receive glucocorticoids. Pharmacologic treatment is recommended in patients (men age ≥50 or post-menopausal women) with a previous osteoporotic fracture, or have a BMD T score of -2.5 or less at either the spine or the femoral neck.

Oral bisphosphonates are recommended as first-line agents to prevent glucocorticoid-induced osteoporosis due their low cost and good safety profile. Common side effects of esophagitis can be minimized by instructing the patients to take the drug with empty stomach and to maintain an upright posture for at least 30min after drug intake. Adverse effects of prolonged bisphosphonates treatment (for more than 3-5 years), including atypical femoral fracture and osteonecrosis of the jaw, have been reported to be rare (<0.01% and <0.001%, respectively). Alternative treatments include antiresorptive agent (denosumab) and anabolic agents (teriparatide and abaloparatide). These injectable agents are generally associated with greater increases in BMD as compared with oral bisphosphonates, but they are more expensive. Third-line agents, such as raloxifene (a selective estrogen receptor modulator) in postmenopausal women or calcitonin can be considered for patients in whom other treatments are contraindicated. When treatment is needed in women of childbearing age, agents such as risedronate and teriparatide that have a shorter-half-life and less retention in bone are generally recommended.

Conclusion

Both OCS and ICS are associated with an increased risk of osteoporosis and fragility fracture in people with asthma. Clinicians should encourage adherence with controller therapies to reduce exacerbation, and optimize dose of ICS to control symptoms. In patients at high risk, they should be given referral for age-appropriate BMD monitory, and routine recommendation for adequate dietary intake of calcium and vitamin D, weight-bearing exercise, maintenance of normal weight, and fall prevention. Osteoporosis should be managed as an important comorbidity, and its prevention and treatment should be addressed explicitly in future asthma guidelines.[6]

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Table 1. Clinical risk factors for osteoporosis[7]

Risk factor
Female sex
Increasing age
History of fragility fracture
Low body weight (<45 kg)
Family history of osteoporosis or fragility fracture
Premature menopause (before age 40) or early menopause (age 40-45)
Low calcium intake
Lack of exercise or sedentary lifestyle
Smoking
Excessive alcohol intake (≥ 3 standard drinks per day)
Lack of sun exposure
Prolonged immobilization

Source: Ip TP, Cheung SKW, et al. The Osteoporosis Society of Hong Kong (OSHK): 2013 OSHK guideline for clinical management of postmenopausal osteoporosis in Hong Kong. Hong Kong Med J 2013; 19 Suppl 2:1-40.

Intranasal corticosteroids: safety and side effects

Dr. Jason Y. K. CHAN

MCHK, MBBS (London), DABOto, FRCSEd (ORL), FHKCORL, FHKAM (Otorhinolaryngology)
Specialist in Otorhinolaryngology
Assistant Dean (Health Systems), Faculty of Medicine, The Chinese University of Hong Kong
Associate Professor, Department of Otorhinolaryngology, Head and Neck Surgery
The Chinese University of Hong Kong

Commonly in medical practice, patients express concern regarding the use of intranasal corticosteroid (INCS) sprays. The word "steroid" immediately raises eyebrows in patients, a medication commonly regarded by the public as having an association with significant side effects. This is followed by poor adherence and a less than ideal treatment for patients with allergic rhinitis or chronic rhinosinusitis. Similar to Dr. Veronica Chan's article in this newsletter on osteoporosis and fragility fractures with inhaled and oral corticosteroids, it is useful to review the current state of affairs of INCS with regards to their common side effects, and side effects that are of particular concern to the patient and physicians.

Types of intranasal corticosteroids

The INCS can typically be divided by their generation, which includes the older first generation such as beclomethasone and budesonide and the newer second generation drugs, mometasone and fluticasone as examples (Table 1). The first generation drugs are known in particular for the significantly higher systemic bioavailability than the second generation drugs.[1]

Common side effects

In children, two of the most common side effects often noted by family and physicians include headaches and epistaxis. A recent systematic review and meta-analysis demonstrated that in 16 randomized control trials, there was no statistically significant increased risk of epistaxis[2]. Similarly, with regards to headaches, there was no increased incidence of headaches when using INCS.

In adults, the picture is slightly different, although the two most common side effects are also headaches and epistaxis. Patients using INCS were at a significantly higher risk of developing epistaxis when compared to controls, with a relative risk of 1.56 based on a recent meta-analysis.[3] This is consistent with previous studies, in particular a Cochrane review from 2016 that looked at INCS in patients with chronic rhinosinusitis, where the relative risk was 2.74 when compared to placebo and no intervention[4]. However, on caveat is that most studies do not document that all participants were taught the proper techniques of using INCS. In regard to headaches, there was no significant difference in the incidence of headaches with the use of INCS when compared to placebo.

Specific side effects

Raised intraocular pressure

The use of INCS leading to the development of raised intraocular pressure (IOP) is controversial. Furthermore, whether this translates into clinically relevant presentation of glaucoma is also debatable. Most recent studies looking at the second generation of INCS suggest that they do not result in raised intraocular pressure.[3] A meta-analysis evaluating IOP showed that in 4 assessable randomized clinical trials, there was no significant increase in intra ocular pressures.[5] A further systematic review revealed the absolute increased incidence of raised IOP was 0.8% that was not significant. In addition, evaluating for the presence of glaucoma following starting treatment of INCS the overall incidence was 0.1% that was not significant. Studies on patients with existing glaucoma and the use of concomitant INCS, particularly in regard to the management and control of their glaucoma, is lacking. Therefore, in a patient with glaucoma and the need for INCS, second generation INCS can be used, but closer monitoring of the IOP could be considered given the theoretical risk of raised IOP.

Hypothalamic-pituitary-adrenal axis suppression (HPA) – growth velocity

In children, there has long been a concern about the effects of INCS on the HPA and growth velocity. However, the evaluation of the impact of long-term use of INCS on growth velocity has been hampered by the large heterogeneity between studies. A systematic review suggests there may be short-term growth velocity retardation, with normal growth rates after discontinuation.[2] However, many of the studies evaluated were over 10 years old and predominantly investigated the first generation INCS, whereas, for example, beclomethasone is known to have a high bioavailability and associated with a significant reduction in growth. More studies are needed on the newer second generation INCS to review if this effect still holds, given their lower bioavailability. There are also no studies evaluating catchup growth and on final adult height after the discontinuation of INCS. Therefore, further work is needed to understand the current role of INCS on HPA and growth velocity in children.

In adults, there was no significant HPA noted, and longitudinal growth velocity is not applicable in the adult population.

Conclusion

In children, INCS used as directed is, in general, safe. Growth velocity represents the main unknown factor

where further study is needed. HPA axis and visual changes are rare. The incidences of epistaxis and headaches are also not increased. In adults, the most common side effect is epistaxis, and otherwise it is generally safe.

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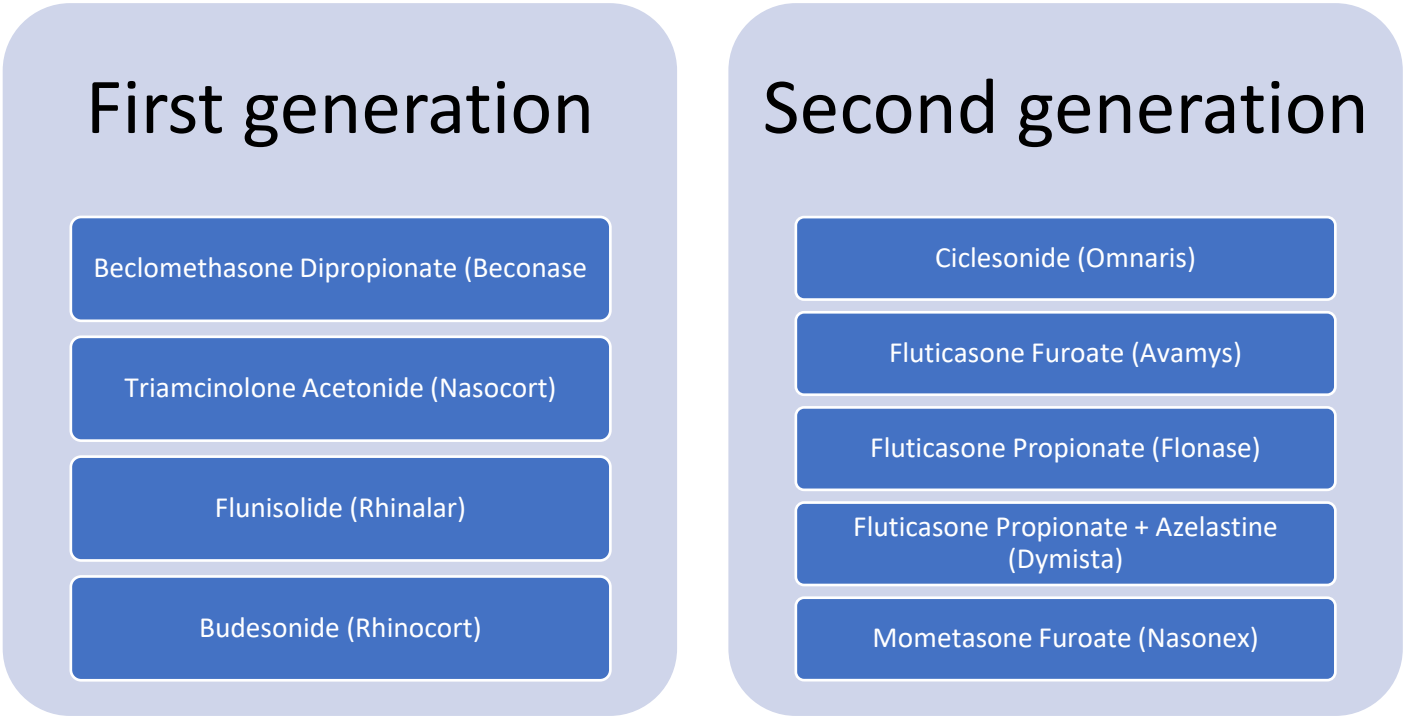
Figure 1. Table of first and second generation INCS. With first generation having more systemic bioavailability compared to the second generation INCS.[1]



Post-COVID-19 new allergies

Dr. Polly P.K. HO

MBBS, MRCPCH, FHKCPaed, FHKAM(Paed)
Specialist in Paediatric Immunology, Allergy and Infectious Diseases
Associate Consultant, Department of Paediatrics, Queen Elizabeth Hospital

The media has brought to our attention in September of this year the observation that a woman in the United Kingdom who had recovered months after COVID-19 infection and then developed an allergic reaction towards a hair dye despite using the same product for decades.[1] She described her whole scalp with feelings of a burning sensation and a rash, and subsequent atopy patch testing was positive. UK's National Hair and Beauty Federation member survey found that amongst 71 respondents, 10 clients reported experiencing an unexpected allergic reaction to hair dyes this year. Among those, three clients had previously contracted COVID-19. Thus, the Federation posted a reminder to members regarding the importance of conducting allergy alert including allergy alert posters, client information sheets, client allergy test record, and strongly encourages all clients who have contracted COVID-19 to perform a 48-hour patch test.

Another report published earlier this year described a young lady with a delayed hypersensitivity reaction to hyaluronic acid dermal filler post-COVID-19 infection.[2] She had dermal fillers regularly in the same clinic for the past 6 years and her last visit was in February 2020. In December 2020, one month after her COVID-19 infection, she suddenly developed periocular swelling in areas previously injected with dermal filler. The swelling subsided a few days after oral anti-inflammatory treatment. Similar cases of facial swelling with past dermal filler treatment after COVID-19 vaccine administration were reported as well. These cases brought forth the concern of alteration of body's allergic response after a state of hyperinflammation post-COVID.

The link between COVID-19 infection and delayed hypersensitivity was further depicted by a report of a patient with maculopapular lesions and targetoid lesions reminiscent of erythema multiforme, which was likely delayed hypersensitivity as the underlying pathophysiological mechanism in causing cutaneous lesions due to SARS-CoV-2.[3]

COVID-19 infection induces complex immune responses that potentially influence our sensitization and allergic response. The exact etiology of the delayed hypersensitivity reaction following COVID-19 infection remains incompletely understood and further research is in great need.

The immune response towards COVID-19 infection remains one of the major research aspects in the field. There is the school of thought that hyperinflammatory cytokine storms and allergic reactions may be rooted in an atypical response to SARS-CoV-2 by dysfunctional mast cells and mast cell activation syndrome.[4] In COVID-19 infection, the immune response is characterised by proliferation and hyperactivation of T cells, macrophages, natural killer cells and overproduction of more than 150 types of cytokines. Among these, mast cells may play an important role. In fact, lung biopsies from COVID-19 patients clearly showed a significant higher number of activated mast cells, signifying its important role during the infection. In a recent study, mast cell activation symptoms were found to be increased in long-COVID (also known as long-haul COVID and post-acute sequelae of COVID-19) patients and mimicked the symptoms and severity reported by patients with mast cells activation syndrome.[5] Examples of symptoms include hives, face swelling, wheezing, rhinitis and worsening symptoms after ingesting histamine-containing foods. This drives the hypothesis that activation of aberrant mast cells induced by SARS-CoV-2 infection by various mechanisms may cause these chronic post-COVID symptoms. The proposed mechanisms include: 1) complex interactions of stressor-induced cytokine storms with epigenetic-variant-induced states of genomic fragility to induce additional somatic mutations in stem cells or other mast cell progenitors; 2) cytokine or SARS-CoV-2 activation of mast cells and microglia; 3) loss of genetic regulation of mast cells due to dysregulation of genes by SARS-CoV-2; 4) development of autoantibodies that react with receptors on mast cells; 5) increase in Toll-like receptor activity by SARS-CoV-2.

The development of allergic disorders post-COVID signifies that the infection greatly affect the immune and allergy responses. Nevertheless, the pathways leading to new allergies and post-COVID sequelae are likely multifactorial and further research to understand the various mechanisms will certainly carry significant therapeutic implication.

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Topical cyclosporin A in paediatric vernal keratoconjunctivitis

Dr. Allie LEE

MBBS(HK), FCOphth(HK), FHKAM(Ophth), MRCS(Ed)
Specialist in Ophthalmology
Clinical Assistant Professor, Department of Ophthalmology, LKS Faculty of Medicine,
The University of Hong Kong

Allergic eye diseases encompass a wide spectrum of manifestations. While mild forms of disease usually respond well to first-line therapies and supportive measures, more severe forms may result in chronic visual loss and poor quality of life.

Vernal keratoconjunctivitis (VKC) is a severe and potentially debilitating allergic eye disease that typically occurs in school-age children and has a male predominance.[1] The immunopathology of VKC is thought to involve a Th2-mediated allergic mechanism, which triggers a cascade of inflammatory and remodeling processes on the ocular surface. Topical cyclosporin A (CsA), a calcineurin inhibitor, was shown to be effective in controlling ocular surface inflammation in VKC by inhibiting Th2 proliferation and interleukin 2 production. A cationic emulsion formula has been developed to enhance its bioavailability, which has recently been approved by the US Food and Drug Administration (FDA) for the treatment of VKC in children and adolescents.[2]

Current evidence

The safety and efficacy of cyclosporine 0.1% (1 mg/mL) cationic emulsion was evaluated in the VErnal KeratoconjunctiviTIs Study (VEKTIS).[3] It was a multicenter, randomized, double-masked, vehicle-controlled clinical trial in paediatric patients with active, severe VKC. Participants were randomized to CsA four times a day (QID), CsA two times a day (BD) plus vehicle BD and vehicle QID. Significant improvements in VKC symptoms and quality of life were demonstrated in patients treated with CsA over vehicle, particularly in the high-dose group. Most treatment-related adverse events were mild or moderate, the most notable of which being instillation site pain occurring more often in the CsA high-dose group. A follow-up study of the same cohort showed stable improvement at 12 months, together with a favourable safety profile.[4]

Clinical application

The medication is now commercially available as Verkazia®, at the recommended dosage of one drop QID to the affected eye for paediatric patients.[2] In Hong Kong, however, it is not yet a registered pharmaceutical product by the Department of Health.[5] On the other hand, Ikervis®, also a cyclosporine 0.1% emulsion, is readily available. It is important to note that Ikervis is licensed for severe keratitis in adults with dry eye diseases, at a one drop daily regimen.[6] Therefore, its use in VKC and in paediatric patients would be considered off-label. Another common topical cyclosporin, Restasis®, contains cyclosporin 0.05% and is indicated in dry eye diseases (not allergic eye diseases) twice daily.[7] A comparison of these three ophthalmic cyclosporin preparations is summarized in Table 1.

For patients with severe allergic eye diseases not responsive to first-line treatment, further assessment by an ophthalmologist would be useful in ruling out other causes in confirmining the diagnosis and then the most appropriate treatment modality.

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Table 1. Commercially available cyclosporin ophthalmic preparations and their recommended uses.

Agent	Formula	Indication	Age	Frequency	Registration in HK
Verakazia®	Cyclosporin 0.1%	VKC	4-18	4 times/day	No
Ikervis®	Cyclosporin 0.1%	Dry eyes	18+	Daily	Yes
Restasis®	Cyclosporin 0.05%	Dry eyes	16+	2 times/day	Yes

What can we learn from follow-on studies of peanut oral immunotherapy trials?

Dr. Agnes S.Y. LEUNG

MBChB, MRCPCH, FHKCPaed, FHKAM(Paed)
Assistant Professor, Department of Paediatrics, The Chinese University of Hong Kong

Peanut has been recognised as one of the most common elicitors of food anaphylaxis. Peanut allergy typically persists into adulthood and is associated with a high chance of accidental exposure leading to allergic reactions that could be potentially severe. Novel therapeutic approach, in particular oral immunotherapy (OIT), to treat peanut allergy has therefore gained increased traction over the past few years.

In the recent publication on "Open-label follow-on study evaluating the efficacy, safety, and quality of life with extended daily oral immunotherapy in children with peanut allergy", Fernandez-Rivas et al. reported the efficacy, safety or tolerability and food allergy-related quality of life from a follow-on study that evaluated FDA's first approved oral biologic drug (Peanut Allergen Powder-dnfp [PTAH], previously known as AR101) for peanut-allergic children aged 4 to 17 years old.[1] Two phase 3, randomized, placebo-controlled trials have been conducted so far to evaluate the efficacy and safety of daily PTAH treatment. The PALISADE trial involved participants from North America and Europe aged 4-55 years while the ARTEMIS trial involved participants aged 4-17 years from Europe. A follow-up study, ARC004, enrolled participants from the PALISADE trial after the initial treatment phase. This article by Fernandez-Rivas et al. presented data of 142 participants from the start of PALISADE through the end of ARC004 who received daily dosing of PTAH. Participants were grouped into either Group A (daily PTAH for approximately 1.5 years) or Group B (daily PTAH for 2 years).

In terms of efficacy, higher proportion of Group B participants compared with Group A participants were able to tolerate the highest challenge dose of 2000 mg peanut without dose-limiting symptoms (80.8% vs 48.1%). Fewer participants from Group B (3.8%) required adrenaline as rescue medication during the exit double blind placebo-controlled food challenges (Group A 24.0%). This was consistent with the lower mean serum levels of peanut-specific IgE at ARC004 exit observed in Group B compared with Group A participants. In terms of safety, the exposure-adjusted treatment-related adverse events (AEs) decreased from 56.6 events per participant-year during PALISADE initial dose escalation and updosing to 4.7 during ARC004 maintenance in both groups. However, systemic allergic reactions were still a concern, occurring in 4.5% of participants in Group A and in 9.4% of Group B during the therapeutic maintenance in PALISADE and in 6.4% of participants in Group A and 15.6% of Group B during the follow-on phase at ARC004. Despite that, the Food allergy-related quality of life (FAQoL) using age-appropriate FAQLQ and FAIM instruments noted consistent improvements from PALISADE screening to ARC004 exit. It was observed that the percentage of children and teenagers demonstrating clinically meaningful improvement in the FAQLQ total and domain scores (≥0.5) increased with duration of PTAH treatment.

Although peanut allergy remains to be relatively low in most Asian countries, treatment is still essential in this part of the world as peanut allergy tends to bring about significant physical and psycho-social impact to patients and families. Although PTAH primarily aims to induce desensitization (i.e. an increase in reaction threshold to the allergen) but not sustained unresponsiveness to peanut, findings from this article indicated that PTAH treatment is efficacious particularly with an extended duration of treatment, is tolerable and may potentially reduce stress and anxiety. Overall, peanut oral immunotherapy is a promising treatment approach with PTAH demonstrated to be effective in mitigating allergic reactions that may occur with accidental exposure to peanuts. Sustained unresponsiveness to peanut is also achievable by other forms of peanut oral immunotherapy.

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Finding the right DRESS

Dr. Jaime S. ROSA DUQUE

MD (UCI, USA), PhD in Pharmacology and Toxicology (UCI, USA), LMCHK (UCI, USA), DCH (UK), FHKCPaed, FHKAM (Paediatrics), Specialist in Paediatric Immunology Allergy and Infectious Diseases (HK), Diplomate of the American Board of Pediatrics, FAAP, Diplomate of the American Board of Allergy and Immunology, FACAAI, FAAAAI
Clinical Assistant Professor, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a delayed-type adverse drug hypersensitivity, and its severe form is associated with significant morbidity and mortality.[1] In general, there is variable cutaneous eruption, fever, lymphadenopathy, hematologic abnormalities and visceral involvement. Cutaneous manifestation is the most frequent finding, occurring in 99-100% of cases. Often, there is a symmetrical distribution of the maculopapular, morbilliform rash at the trunk and extremities that covers greater than half of the body surface area. The color tends to have a deep red, violaceous or plum hue. However, the rash can also be quite polymorphic, which may include urticaria, pustules, blisters, exfoliative dermatitis and target lesions. Some patients experience pruritus or a burning pain. A facial/ear rash with edema is observed in ~75% of the time. Other clinical features and diagnostic criteria are listed in Table 1.

The pathogenesis for DRESS is thought to involve T cell-mediated and eosinophilic pathways, although little else is known at this time.[1] Genetic predisposition, such as HLA associations, has been found, in which the highest positive predictive value (PPV) has been found for those with HLA-B*57:01 exposed to abacavir, although the PPV is only ~50%. Hence, alleles and their connections with specific medications are not completely or reliably linked to development of reactions.[1] Concurrence with viral reactivation of the *Herpesviridae* family, most often human herpesvirus-6 (HHV-6), but also HHV-7, Epstein-Barr virus and cytomegalovirus, alone, simultaneously or sequentially has been reported, but not always.[1] HHV-6 reactivation is one of J-SCAR's diagnostic criteria for DRESS, but not RegiSCAR or Bocquet (Table 1).[1] This variability highlights the complexity of this disorder. As such, further research to clarify the pathophysiology and diagnostic accuracy are necessary.

Previously, latent infection of monocytes and macrophages by HHV-6 has been demonstrated.[2] During the proliferation phase, genomic replication occurs by preferential activation of T helper cells. OX40, or CD134, is a member of the tumor necrosis factor receptor superfamily. It is expressed predominantly on activated T helper cells and functions as a cellular receptor for HHV-6 entry. The OX40 ligand (OX40L) is expressed on antigen-presenting cells and activated T cells. Interaction of OX40-OX40L is required to generate long-term memory response, optimal T-cell activation and T_H2 differentiation. Upregulation of OX40 and OX40L in CD4+ T cells and peripheral blood mononuclear cells, respectively, have previously been shown in patients with DRESS. Soluble OX40 has anti-inflammatory effects antagonistic towards OX40L. Serum sOX40 levels are abnormal in autoimmune diseases such as systemic sclerosis, rheumatoid arthritis and atopic dermatitis, although the role in DRESS is unknown.

Mitsui and colleagues recently measured serum sOX40 levels in a retrospective, longitudinal study in patients with DRESS (n=39), maculopapular exanthema/erythema multiforme (n=17), Stevens-Johnson syndrome/toxic epidermal necrolysis (n=13), autoimmune bullous diseases (n=5) and healthy controls (n=5) using an enzyme-linked immunosorbent assay (ELISA) kit (IBL, Gunma, Japan).[2] Serum sOX40 levels in patients with DRESS, along with expression of OX40 on CD4+ T cells, were elevated in the acute stage of illness. Serum sOX40 levels were also significantly correlated with DRESS severity. Patients with detectable HHV-6 had higher sOX40 levels than those without HHV-6 infection/reactivation. Serum sOX40 levels were correlated with HHV-6 DNA levels, as quantified by PCR.

The above findings are promising. Serum sOX40 appears to be a potential diagnostic and severity marker for DRESS and HHV-6 infection/reactivation. More research work will be required to determine whether the diagnoses of two outcomes need to be distinguished. Although sOX40 is not readily available in the commercial setting or in the Hong Kong Hospital Authority system at this time, measurement of this cytokine is not labour-intensive. Therefore, if its accuracy and utility are confirmed, inclusion of sOX40 as a biomarker for the diagnosis or severity rating of DRESS may be beneficial in the future.

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Table 1. Characteristics and criteria for diagnosis of DRESS.

RegiSCAR	Bocquet et al	J-SCAR
1. Acute skin eruption	1. A cutaneous drug eruption	1. Maculopapular eruption developing >3 weeks after starting drug(s)
2. Fever (>38°C)	2. Systemic involvement:	2. Prolonged clinical manifestations 2 weeks after discontinuation of the causative drug
3. Lymphadenopathy at ≥2 sites	lymphadenopathy ≥2 cm (diameter), or	3. Fever (>38°C)
4. Involvement of at least 1 internal organ	hepatitis (transaminase ≥2x upper limit, or	4. Liver (alanine aminotransferase >100 U/L), renal or other organ involvement
5. Lymphocytosis or lymphocytopenia	interstitial nephritis, or	5. Leukocyte abnormalities (at least 1 present):
6. Peripheral eosinophilia	interstitial pneumonitis, or	leukocytosis (>11 × 10^9 /L)
7. Thrombocytopenia	carditis	atypical lymphocytosis (>5%)
	3. Hematologic abnormalities:	eosinophilia (>1.5 × 10^9 /L)
	eosinophilia ≥1.5×10^9 /L, or	6. Lymphadenopathy
	presence of atypical lymphocytes	7. HHV-6 reactivation
At least 3 characteristics required (additionally, a scoring system can be applied to determine definite, probable or no case)	All 3 characteristics required	All characteristics required for typical cases and first 5 for atypical cases

Emerging treatment option for moderate-to-severe atopic dermatitis: JAK inhibitors

Dr. Christina S.M. WONG

MBBS, MRCP, FHKCP, FHKAM
Specialist in Dermatology and Venereology
Associate Consultant, Division of Dermatology, Department of Medicine, Queen Mary Hospital

Refractory AD and life burden

Severe uncontrolled atopic dermatitis (AD) often causes unrelenting itch, which results in skin-related complications such as excoriation, infection and disfigurement. AD also affects multiple aspects of patients' lives that are not always apparent. Many patients struggle with daily living due to repeated hospitalization, sleep disorder and depression-anxiety disorder. These can magnify into significant impact on one's social and sexual relationship, change in lifestyle, reduced quality of life, frequent absentees from school, work productivity loss, high health care cost and economic consequences.

Unmet need for effective treatment

AD patients are desperate for effective treatment to achieve symptoms relief, long-term control, flare reduction and prevention of complications. However, topical treatment alone unlikely provide adequate control in moderate-to-severe AD. Current systemic therapies for moderate-to-severe AD include conventional non-biologic treatment and biologic treatment. Non-biologic treatments include cyclosporine, methotrexate, azathioprine, mycophenolate and prednisolone, all of which have risks of organ damage and other potential side effects need to be monitored regularly (Table 1). Biologic treatments include the interleukin (IL)-4/13 inhibitor (dupilumab), IL-13 inhibitors (tralokinumab, lebrikizumab) and the IL-31 inhibitor (nemolizumab). These target cytokines and their receptors, which are generally safer and more effective. Yet, with a wide array of options, only a minority of moderate to severe AD patients have ever received systemic treatment. This may be due to multifactorial causes, such as safety, efficacy and its sustainability, dosing regimen, route of administration and high costs, leading to an overall undertreatment of AD. Overall, these impediments result in a significant unmet need.

JAK inhibitors – a new class of drugs for moderate-to-severe AD

The Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway is one of the major regulators of immunity and myeloproliferation.[1] Advanced understanding of this pathway has led to the development of targeted inhibitors against Janus kinases as a class of new drugs. The JAK inhibitors (JAKIs) effectively treat a multitude of hematologic and inflammatory diseases with great success.

JAK-STAT pathways are pivotal for downstream signalling of inflammatory cytokines including interleukins, interferons and growth factors, which can contribute to autoimmune skin disorders.[2] In AD, besides the predominance of CD4+ T cell infiltrates in AD lesions, lesional skin is characterised by an over-expression of inflammatory T-helper (Th) 2 cytokines (IL-4, IL-13, IL-31).[2] The JAK-1 mediated Th2 cytokines, IL-4 & IL-13, negatively affect the skin barrier integrity by inhibiting the expression of filaggrin and loricrin. IL-22 is elevated in AD lesions, which is associated with epidermal thickening and skin barrier disruption.[2] It potently induces the expression of neuropeptide in dermal layers that positively correlates with the scratching behaviour.

Ongoing research and studies provide clinical data on the safety and efficacy of JAKIs in the treatment of moderate-to-severe AD, supporting that JAKI is an effective alternative to conventional therapies.[1] JAKIs belong to a drug class of small molecules that target the same family of kinases, but each has distinct differences in its chemical structures and pharmacologic properties, contributing to different potency/selectivity towards individual JAK isoforms. Updacitinib and abrocitinib have higher selectivity towards JAK1 versus JAK2, JAK3 and tyrosine kinases 2 (TYK2), while baricitinib has higher selectivity towards JAK1 and JAK2 than TYK2 and JAK3.[3]

Pivotal clinical trials and prevailing results

In a pivotal clinical trial on upadacitinib, Measure-Up 2, 60 % and >70% of patients achieved EASI75 (75% reduction in clinical severity of AD by eczema area and severity index EASI) after taking 16 weeks of upadacitinib 15 mg daily and 30 mg daily respectively, compared to only 13% in the placebo group.[4] If combined with topical corticosteroid (TCS), 65% and >75% of patients achieved EASI 90 (90% reduction in clinical severity) in the upadacitinib 15 mg and 30 mg daily groups, respectively, compared to only 26% in the placebo group with TCS.[5]

For the long-term efficacy assessment, 80% and 85% patients in the upadacitinib 15 mg and 30 mg daily groups, respectively, achieved EASI75 when they extended the duration of treatment up to 52 weeks. Similar results have been shown in patients taking another JAK1 inhibitor, abrocitinib, of which 45% and >60% of patients in the 100 mg and 200 mg daily dosing groups, respectively, achieved EASI75 at week 12 in another study.[6] Finally, in a trial investigating baricitinib combined with TCS, 43% and 48% patients achieved EASI75 at week 16 with 2 mg and 4 mg daily dosing, respectively, compared to 23% in the placebo arm.

However, a relatively lower proportion of patients (18% and 25%) achieved EASI75 on the baricitinib (2 mg and 4 mg) alone regimen, compared to 6% in the placebo arm.[7]

In summary, baricitinib, abrocitinib and upadacinib have all demonstrated efficacy at reducing skin lesions and itch in AD patients at weeks 12 and 16, and efficacy was maintained at least up to 52 weeks. Although there is no head-to-head trials between JAKIs, efficacy seems to differ across individual JAKIs. Based on the data provided from current studies, and our own experience in using upadacitinib in our clinical trials, upadacitinib seems a promising treatment in moderate-to-severe AD.

Common adverse events of JAKI

In regard to safety, JAKIs are generally well tolerated, though common adverse events (AEs) differ between JAKIs, with some dose-dependency. The most common AEs are acne, headache, non-invasive infections (upper respiratory infections and herpes simplex infections), creatinine phosphokinase (CPK) elevation, increases in cholesterol levels, nausea and diarrhoea.[3-7]

Use of JAKI in moderate-to-severe AD

The European Medicine Agency EMA has extended the indication of abrocitinib and baricitinib, which have already been approved for severe rheumatic arthritis refractory to methotrexate, for the treatment of moderate-to-severe AD in adults. Since August 2021, the European Commission has approved the use of upadacitinib as the first JAKI in the European Union for the treatment of moderate-to-severe AD in adults and adolescents ≥12 years whose skin condition qualifies for systemic therapy. The recommended dose for upadacitinib is 15 mg daily in adolescents and adults. The higher dosing regimen (30 mg daily) is reserved for adult patients who have high disease burden or inadequate response to the 15 mg dosing. JAKI can be used with TSC or topical calcineurin inhibitors in sensitive areas such as face, neck and intertriginous/genital areas. Patients who are pregnant or planning for pregnancy and lactating mothers are currently contraindications for taking JAKIs. Pre-screening for latent tuberculosis and hepatitis status is warranted. At this time, JAKIs have not yet been approved for AD in Hong Kong.

In summary, JAKIs represent a new class of drugs that can effectively treat moderate-to-severe AD. Its long-term efficacy and safety will need to be monitored. With more real-life post-marketing data available in the future, we will have more insight on the long-term use in suitable candidates.

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Table 1. Current and emerging systemic therapies for moderate-to-severe AD.

Therapies	***Non- Biologics***	***Biologics***	***Small Molecule***
Advantage / Disadvantage	Risk of organ damage	Target cytokines and receptors	Target signalling of various cytokines
	Long-term safety profile well documented	Safer, more effective	Safer, more effective
Cost	Cheaper	More expensive	More expensive
Drugs	Cyclosporine	IL-4/IL-13 inhibitor (dupilumab)	JAK1 inhibitor (abrocitinib, upadacitinib)
	Methotrexate	IL-13 inhibitors (tralokinumab, lebrikizumab)	JAK1/JAK2 inhibitor (baricitinib)
	Azathioprine	IL-31 inhibitor (nemolizumab)	
	Mycophenolate		

IL: interleukins

Biologics: promising treatments in asthma

Ms. Charlie C. Y. MAK

BPharm (HKU)
Registered Pharmacist (HK)
Resident Pharmacist, Department of Pharmacy, Queen Mary Hospital

Mr. Andrew W.T. LI

BPharm (HKU), MClinPharm (HKU)
Registered Pharmacist (HK)
Clinical Pharmacist, Department of Pharmacy, Queen Mary Hospital

Asthma is a chronic airway inflammation disorder that is characterized by variable airflow limitation. Among all asthma patients, approximately 3-10% are found to have severe asthma. According to the Global Initiative for Asthma (GINA), severe asthma refers to asthma that is uncontrolled in spite of adherence to optimized high-dose inhaled corticosteroids (ICS) and long-acting beta-2 agonists (LABA) treatment and treatment of contributory factors, or when high dose therapy is stepped down, the condition worsens.[1] Asthma is categorized into two endotypes, type 2 (T2) high or T2 low. T2 high asthma involves T-helper cell type 2 (Th2) $CD4^+$ lymphocytes and innate lymphoid cells-type 2 (ILC2s) which secrete interleukin (IL) 4, 5, 9 and 13. There is also secretion of IgE by B cells in the cascade.[2-3] Precision medicine has been established to target T2 high asthma and modulates specific inflammatory pathways.[4]

Currently, there are 5 biologics approved by the United States Food and Drug Administration (FDA) for the treatment of severe asthma, namely omalizumab, mepolizumab, dupilumab, benralizumab and reslizumab. All except reslizumab are registered in Hong Kong. Therefore, the following discussion will focus on those that are available in Hong Kong now. This article reviews the mechanism of action, approved indications, outcome improvement and dosing regimens of biologics for asthma.

Anti-IgE agent: omalizumab

Omalizumab is a humanized anti-IgE monoclonal antibody that prevents IgE from binding to receptors on mast cells and basophils, thus reducing the release of proinflammatory mediators. In addition, the lack of engagement by IgE downregulates the cellular IgE receptors. Downstream allergic response and inflammation are reduced.[2] It is approved for moderate to severe persistent allergic asthma in adults and paediatric patients with symptoms that are inadequately controlled with inhaled corticosteroids.[5] The phase III trial of omalizumab as add-on to severe allergic asthma demonstrated a reduction of 48% in the average number of asthma exacerbation compared to placebo.[6] The INNOVATE study was conducted among patients who had severe persistent asthma even with optimized therapy. Add-on omalizumab reduced asthma exacerbation that required systemic corticosteroids by 26% and reduced severe exacerbation by 50%, when compared to placebo. There was also approximately 0.1 L increase in FEV_1 for the omalizumab group relative to placebo.[7]

Anti-IL-5 agents: mepolizumab and benralizumab

Anti-IL-5 monoclonal antibodies reduce eosinophilic inflammation, as IL-5 is responsible for recruiting and activating eosinophils. Mepolizumab neutralizes and prevents IL-5 from binding to IL-5 receptors, while benralizumab inhibits IL-5 receptors on eosinophils and basophils.[2] Mepolizumab is indicated as add-on maintenance treatment of adult and paediatric patients with severe eosinophilic asthma.[8] In the phase III trial MENSA, subcutaneous mepolizumab reduced the annual rate of asthma exacerbation by 53% in patients, compared to placebo.[9] The SIRIUS trial showed a median reduction of 50% in daily oral glucocorticoid dose from baseline in severe eosinophilic asthma patients using mepolizumab. The overall odds ratio for oral glucocorticoid reduction was 2.39 in the mepolizumab group.[10]

Benralizumab targets IL-5α receptor and induces antibody-dependent cell-mediated cytotoxicity of eosinophils and basophils, thus depleting these cells.[2] It is indicated for add-on maintenance treatment of patients with severe eosinophilic asthma.[11] The phase III trial SIROCCO demonstrated the current recommended dosing of benralizumab was able to decrease the annual rate of asthma exacerbation by up to 51% in severe, uncontrolled asthma with eosinophilia (blood eosinophil counts ≥300 cells per μL) relative to placebo. There was also 0.159 L increase in prebronchodilator FEV_1 in comparison with placebo.[12] In the ZONDA trial, the benralizumab group had a 75% reduction in oral glucocorticoid doses from baseline as compared to 25% in the placebo group.[13]

Anti-IL-4/IL-13 agent: dupilumab

Dupilumab binds to IL-4α receptor and blocks both IL-4 and IL-13 signalling, thereby inhibiting IgE production and inflammatory cells recruitment. Airway hyperresponsiveness and mucous overproduction are

suppressed.[2] This therapy is approved for adults and adolescents as add-on maintenance treatment for severe asthma with T2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO).[14] In the phase III trial LIBERTY ASTHMA QUEST, the reduction in annual severe asthma exacerbation was 48% with dupilumab, while that for patients with higher baseline eosinophils level (blood eosinophil count of 300 or more per cubic millimetre) was 66%, compared to placebo. Subgroup analysis also indicated a greater benefit of dupilumab for patients with a higher baseline FeNO level (≥25 to <50 ppb or ≥50 ppb) than those with the lower value with respect to the exacerbation rate. The increase from baseline FEV_1 was 0.13- 0.14 L greater than placebo group in the overall trial population. Greater benefits in FEV_1 improvement were observed in patients with higher baseline eosinophil and FeNO levels as well.[15] The LIBERTY ASTHMA VENTURE trial suggested dupilumab reduced glucocorticoid dose by 70% relative to 42% in the placebo group.[16]

Selection of biologics

At present, there are no head-to-head comparisons between these biologics. Patient characteristics and predictive biomarkers may help with making an informed decision. Apart from the phenotypes and outcome improvement as aforementioned, factors shown in the table below (Table 1) are of paramount importance when choosing the appropriate biologic.

Once a biologic is started, response should be reviewed in 3 to 4 months. Currently, there is no well-defined evaluation for good response. However, relevant aspects include symptom control, frequency and severity of exacerbation, adverse effect profile and lung function. Ongoing add-on biologic and other asthma medication should be re-evaluated every 3 to 6 months. In cases with good response to biologic use, it is recommended that medication withdrawal should be considered after at least 12 months of treatment.[1]

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Table 1

	Omalizumab (Xolair®)	Mepolizumab (Nucala®)	Dupilumab (Dupixent®)	Benralizumab (Fasenra®)
Approved ages	≥ 6 years old	≥ 6 years old	≥ 12 years old	≥ 12 years old
Route of administration	Subcutaneous			
Dosing	75- 375 mg every 2 or 4 weeks, depending on pre-treatment serum IgE level and body weight	6- 11 years old: 40 mg every 4 weeks ≥ 12 years old: 100 mg every 4 weeks	Initial dose of 400 mg followed by 200 mg every other week, **OR** Initial dose of 600 mg followed by 300 mg every other week	30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter
Approved comorbid conditions	• Treatment of nasal polyps in adult patients • Treatment of chronic spontaneous urticaria in patients ≥ 12 years old	• Treatment of chronic rhinosinusitis with nasal polyps in adult patients • Treatment of eosinophilic granulomatosis with polyangiitis in adult patients • Treatment of hypereosinophilic syndrome in patients ≥ 12 years old	• Treatment of chronic rhinosinusitis with nasal polyposis in adult patients • Treatment of moderate-to-severe atopic dermatitis in patients ≥ 6 years old	• None
Injection recommendation	Administered by healthcare providers only	Can be administered by patients or caregivers	Can be administered by patients or caregivers	Administered by healthcare providers only

Ask the Expert

Prof. Ting Fan LEUNG

MB ChB (CUHK), MD(CUHK), MRCP(UK), FRCPCH, FHKCPaed, FHKAM(Paediatrics)
Specialist in Paediatrics
Professor, Department of Paediatrics,
Prince of Wales Hospital, The Chinese University of Hong Kong

Dr. Agnes S.Y. LEUNG

MB ChB (CUHK), MRCPCH (UK), FHKCPaed, FHKAM (Paediatrics)
Assistant Professor, Department of Paediatrics
Prince of Wales Hospital, The Chinese University of Hong Kong

Dr. Christine Y.Y. WAI

BSc (First Class), PhD (CUHK)
Research Associate, Department of Paediatrics
Prince of Wales Hospital, The Chinese University of Hong Kong

Ms. Chloris H.W. LEUNG

APD (DA), AD (HKAAD)
Senior Research Assistant (Dietitian), Department of Paediatrics
The Chinese University of Hong Kong

Ms. Ann W.S. AU

APD (DA)
Research Assistant (Dietitian), Department of Paediatrics
The Chinese University of Hong Kong

Fish and shellfish allergies in Hong Kong

This section aims to provide up-to-date, evidence-based yet easy-to-understand allergy information to our Nursing and Allied Health (NAH) members. In this issue we have invited the allergy team from the Chinese University of Hong Kong to discuss about fish and shellfish allergies.

Q: What is the prevalence of fish and shellfish allergies in Hong Kong, and how are these data compared to the rest of the world?

A: Shellfish includes two main categories: crustacean (shrimp, crab, etc.) and mollusk (clam, oyster, etc.). According to the EuroPrevall-INCO Survey, shrimp allergy defined by allergic history and positive IgE sensitization was the top food allergies in Hong Kong children aged between 6 to 11 compared to mainland China and neighboring Asian countries (Hong Kong 1.05% vs. Guangzhou 0.18% vs. Shaoguan 0.65% vs. Russia 0.02% vs. India 0.00%).[1] Comparing data from the US, the overall prevalence of shellfish allergy in children was 1.3%, with crustacean at a prevalence of 1.2% and mollusk at 0.5% respectively.[2] Based on self-report, the prevalence of shellfish allergy in children aged 5-17 years was 5.5% in France, whereas in the African region, shrimp allergy prevalence in 5-16 years old children was 0.1 %.[3] While no local data are available for adults, a Vietnam study reported prevalence of doctor-diagnosed shellfish allergy at 2.95% aged between 16-50, ranked as the top of all allergies, compared to 0.7% (crustacean) of self-reported prevalence in the US and 3.3% (shrimp), 2.3% (crab) and 1.5% (mollusk) clinician-diagnosed prevalence in Taiwan.[3,4]

Fish allergy is less common in Hong Kong than shellfish allergy. Still, its prevalence (0.02%) came in second when it was defined by allergic history with positive SPT or sIgE result in the EuroPrevall-INCO Survey.[1] Previous surveys also suggested a 0.19-0.32% self-reported prevalence and a 0.25% doctor-diagnosed prevalence of fish allergy in the local children population.[5,6] These are relatively low when compared to the self-reported prevalence rates from other Asian countries and cities (Vietnam: 1.55-3.71%; Thailand: 0.29-1.1%; the Philippines: 2.29-4.3%; Singapore: 0.26%; Taiwan: 1.32%; Korea: 0.32-0.4%; Japan: 0.3-0.5%), as well as those from most countries in the rest of the world (0-7%).[3,4,7,8]

Q: Do patients commonly outgrow from fish and shellfish allergies?

A: Compared to milk, egg, soy or wheat allergy, from which up to 85% of children can outgrow, only 15% to 20% of children may eventually tolerate fish or shellfish.[9] Some mechanisms implicated in developing tolerance include active regulation by Tregs, and clonal deletion and anergy of T cells, though this is not vigorously studied for fish and shellfish allergies.[10]

A Swedish study reported only 15% of fish-allergic children were able to develop complete tolerance in 2-5 years.[11] Another study in Greece found a slightly higher rate of children outgrowing from fish allergy, with 22% being able to tolerate multiple types of fish (including tuna, swordfish and codfish) as tested by oral food challenges, in 8 years on average since their first reaction to fish.[12] The same study also suggested that complete tolerance was most likely to be developed around adolescence (45.5%).

Q: When one is allergic to a certain kind of fish or shellfish, can they try other types of fish and shellfish?

A: Although a majority of fish- and shellfish-allergic patients are sensitized to the major fish allergen parvalbumin and shellfish allergen tropomyosin, respectively, clinical symptoms to different fish and shellfish species vary considerably in symptoms, intensity and frequency in patients. Clinically, we are also seeing patients tolerating other types of fish and shellfish despite of being allergic to a particular type of seafood. For example, patients allergic to grass carp have been shown to tolerate salmon in a double-blind, placebo-controlled food challenge in our clinic.[13] Our patients also reported tolerating mollusks (e.g. scallop and clam) while allergic to crustaceans (e.g. shrimp and crab), or vice versa.

There are several plausible explanations to this clinical observation: (1) the degree of protein sequence homology across different seafood species, by which crustacean tropomyosins are >90% similar while tropomyosins of crustaceans and mollusks are only 77% similar on average; (2) the difference in content of the major allergens in different seafood species and variation in the amount of parvalbumin in salmon, trout, cod, carp, mackerel, herring, redfish and tuna could range from severalfold to hundredfold. [14,15]

Findings from our studies have shown that use of novel diagnostic tests utilizing component-resolved diagnostics (CRD) can enhance specificity in the diagnosis of seafood allergy. With the use of CRD in combination with oral food challenges, we were able to re-introduce certain fish and shellfish species to a proportion of fish and shellfish-allergic individuals' diets, respectively. However, it is advisable to consult an allergist to arrange appropriate allergy testing against different fish and shellfish species. Self-introduction at home without proper testing can be dangerous with risks of allergic reactions with varying degrees of severity.

Q: Does fish or shellfish allergenicity change due to various food processing methods?

A: Different food processing methods would have different effects on the allergenicity of fish and shellfish. For instance, thermo processing usually have no effect on the allergenicity of seafoods considering the heat-stable property of the major fish allergen parvalbumin and major shellfish allergen tropomyosin. Studies have shown that the allergenicity of seafood can remain unchanged even upon extensive heating at 90 C for 3 hours despite of a change in protein content in the seafood. In some examples, extensive heating might also lead to increased allergenicity of seafood that could be due to concentrated allergens and/or dimerization of parvalbumin/tropomyosin.

However, other food processing methods could lead to reduction in allergenicity of seafood. Fermented foods such as saeujeot, a salted and fermented shrimp product popular in Korea, was shown to have reduced IgE binding that might be caused by the activity of a trypsin-like enzyme that decomposes tropomyosin during the fermentation process.[16] Another example is the total loss of allergenicity of canned tuna comparing to fresh tuna as a result of extreme temperature and pressure during the canning process, by which a study from Norway reported that no definable protein and so IgE-reactive allergen could be detected in the canned tuna sample.[17]

Q: Apart from dietary avoidance, is desensitization possible for fish and shellfish?

A: Unlike peanut, cow's milk and egg allergies with oral, sublingual and epicutaneous immunotherapy being investigated, there is to date no licensed immunotherapies available for seafood allergy. Hence, strict avoidance remains the most effective management strategy. Meanwhile, only a few clinical case studies suggested the possibility of inducing desensitization to fish in individual patients by subcutaneous immunotherapy with codfish extract solution, or oral immunotherapy using swordfish, hake, or codfish.[18,19,20,21] One study showed more promising results; successful desensitization was seen in all 9 fish-allergic patients after following a sublingual-oral desensitization protocol using boiled codfish.[22] Another study in Egypt reported that daily sublingual shrimp extract dosing for six months led to significant reduction in IgE level and increased IgG level in all 60 shrimp allergic subjects.[23] But this study did not include any placebo control or end-point food challenge results, so efficacy of desensitization of this intervention is still inconclusive. Moreover, an animal study showed that administration of low dose recombinant shrimp tropomyosin favors the induction of tolerance in mice, [24] but its efficacy and therapeutic potential is yet to be investigated in human trials.

Q: What are the advances in treating fish and shellfish allergies?

A: Quite a number of studies have been conducted to evaluate the efficacy and safety of different novel methods for treating seafood allergies over the past decade.[25,26] For example, the elucidation of T-cell epitopes of shrimp tropomyosin led to the development of six immuno-regulatory peptide vaccines, and a

mixture of these peptide vaccines as oral immunotherapy resulted in robust down-modulation of allergic inflammation to shrimp in mice accompanied by significant increase in tolerogenic immune responses.[27] Two hypoallergens of shrimp tropomyosin (MEM49 and MED171) were also developed. When formulated as DNA vaccines, both of them demonstrated effectiveness in reducing shrimp allergy in the animal model.[25] This study also showed that DNA vaccination led to increase in regulatory T cells with transferable immuno-regulatory effects, thus suggesting the plausible induction of longer term sustained unresponsiveness by this intervention rather than merely desensitization in the recipients.

In the Food Allergy Specific Immunotherapy (FAST) project, hypoallergenic recombinant parvalbumin was designed for treating persistent and severe allergy to fish (cod).[28] When immunizing mice with the mutated parvalbumin of cod (mCpy c 1), blocking IgG antibody was induced that inhibited IgE binding to cod parvalbumin and parvalbumin-induced basophil degranulation.[29] This hypoallergenic parvalbumin also reduced allergic symptoms caused by fish allergen challenge in the animal model. Although all these strategies are still at the experimental stages, it might be just a matter of time when we achieve a cure for seafood allergy.

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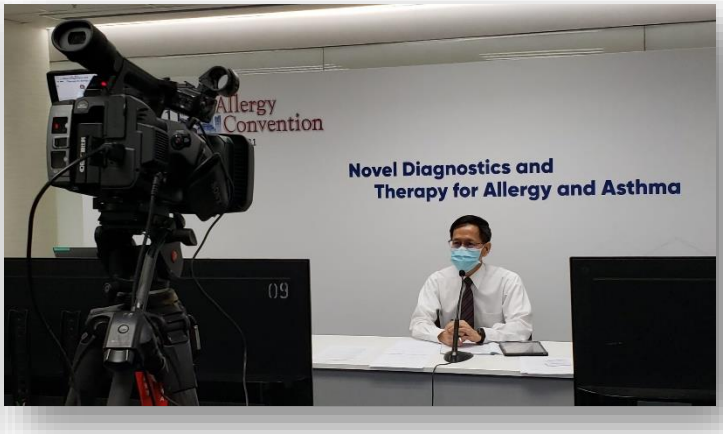
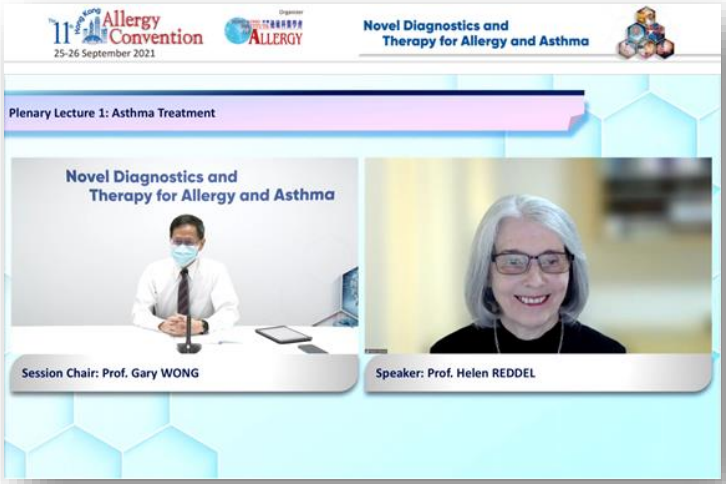
11th Hong Kong Allergy Convention (HKAC 2021)

Date: 25 – 26 September 2021 (Sat – Sun)

Opening Ceremony



Plenary Lecture 1: Asthma Treatment



Plenary Symposium 1: Novel Treatments for Allergic Diseases and Immunodeficiency

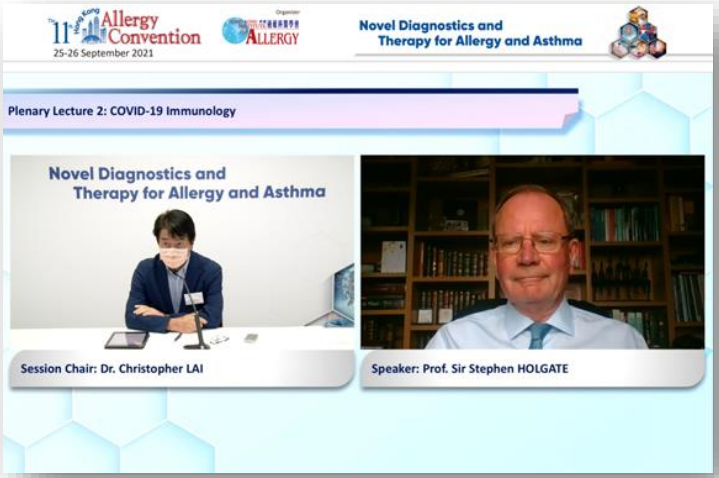
Symposium 1

EAACI Symposium: Food Allergy

Symposium 2

Symposium 3

Plenary Lecture 2: COVID-19 Immunology



Plenary Lecture 3: COVID-19 Pandemic

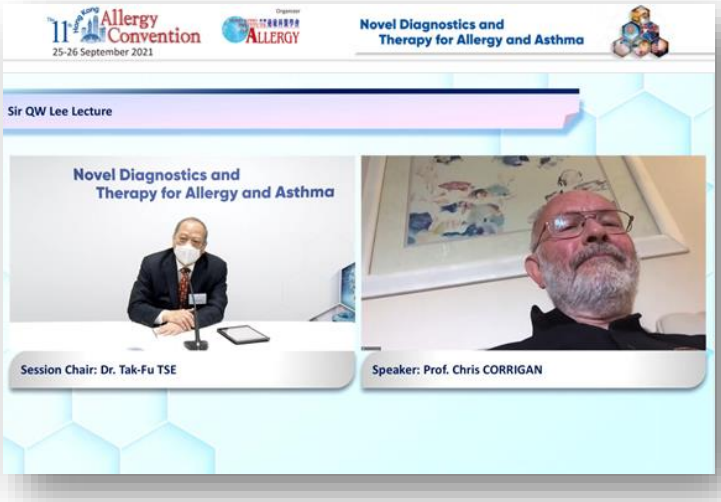
ACAAI Symposium: Asthma

Lunchtime Symposium

Plenary Symposium 2: Allergic Diseases: From Mechanisms to Clinical Management

Plenary Symposium 3: COVID and Allergy

Sir QW Lee Lecture



Symposium 4

Memorable Moments

Overseas Meetings

EAACI 2022 (European Academy of Allergy and Clinical Immunology 2022)
1 - 3 July 2022 / Prague, Czech Republic (https://www.eaaci.org/eaaci-congresses/eaaci-2022)

ERS 2022 (European Respiratory Society (ERS) International Congress 2022)
4 - 6 September 2022 / Barcelona, Spain (https://www.ersnet.org/congress-and-events/congress/)

APAAACI 2022 PSAAI@50
1 - 4 October 2022 / Manila, Philippines (https://www.apaaaci.org/2022)

CHEST 2022 (The American College of Chest Physicians Annual Meeting 2022)
16 - 19 October 2022 / Nashville, Tennessee, USA (https://chestmeeting.chestnet.org/)

ACAAI 2022 (American College of Allergy Asthma and Immunology Annual Scientific Meeting 2022)
10 - 14 November 2022 / Louisville, Kentucky, USA (https://annualmeeting.acaai.org/2022/)

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