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Personalised Care in Respiratory Medicine

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References: 1. Watz H, Troosters T, Beeh KM et al. Int J Chron Obstruct Pulmon Dis. 2017 Aug 24;12:2545-2558. **2.** Duaklir® Genuair® Hong Kong Packaging Insert. Aug 2015. **3.** Singh D, Jones P, Bateman E, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC Pulm Med. 2014;14:178. **4.** Bateman ED, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res. 2015 Aug 2;16:92.

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LABA= Long-acting β2-adrenergic agonist. LAMA= Long-acting muscarinic antagonist.
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The Cover Shot

Sunrise at the Hemu Village (禾木村), located inside the Kanas Nature Reserve in Altay Mountain area in Northern Xinjiang. According to the China National Geographic Magazine, Hemu Village is one of the most beautiful villages in China. Other scenic attractions include the Wolong Bay, Immortal Bay, Moon River, Kanas Lake and Baihaba Village.

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Editorial

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There have been revolutionary advances in the treatment of respiratory diseases in the past few decades. Not only are the treatments more potent and effective, they are also more specific to cater for the phenotypic and genotypic characteristics of the individual. Such revolutionary developments have been observed in the treatment of lung cancer, airway diseases and sleep apnoea, as well as in the field of interventional pulmonology. In this issue of the Hong Kong Medical Diary, we have invited renowned local experts to give us the most contemporary update and development in the personalised management of respiratory diseases.

In Chronic Obstructive Pulmonary Disease (COPD), Dr Thomas YW MOK reviewed different COPD phenotypes based on (1) symptoms and exacerbations, (2) asthma/chronic bronchitis features and (3) level of blood eosinophil. Pharmacological treatments are matched according to the phenotypic characteristics of COPD patients to attain the most significant and optimal responses.

Phenotyping is particularly important in the management of severe asthmatic patients who are already on high-dose inhaled corticosteroids. Dr KP CHAN and Dr Fanny WS KO reviewed the pathophysiological basis of the type II inflammation and the various tests to differentiate type II from non-type II inflammation. Type II phenotype-based biological treatments such as anti-IgE (omalizumab), anti-IL5 (mepolizumab, reslizumab and benralizumab), anti-IL4 (dupilumab) were introduced. Treatments options for non-type II asthmatic patients were also discussed.

As for the contemporary treatment of advanced stage non-small cell lung cancer (NSCLC), molecular testing on epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1 rearrangment or its expression, BRAF mutation as well as programmed death ligand 1 (PD-L1) expression has played a critical and crucial role to determine the subsequent treatments. Dr WC KWOK and Dr David CL LAM gave us an excellent review of the biologic treatments including (1) tyrosine kinase inhibitors (TKIs) targeting EGFR mutations; (2) treatment of TKI-resistant NSCLC; (3) TKI-targeting ALK mutations; (4) treatment for ROS1 rearranged NSCLC; (5) treatment of BRAF-mutated NSCLC and (6) immunotherapy targeting at anti-programmed cell death 1 (anti-PD1) and anti-programmed death receptor-ligand 1 (anti-PDL1).

In the field of interventional pulmonology, Dr Bing LAM summarised the latest endoscopic technologies applied in making a diagnosis of peripheral lung lesion and mediastinal lesion. The use of bronchoscopic interventions in airway disease such as thermoplasty and endobronchial lung volume reduction using valves, coils and vapour were also discussed. For obstructive sleep apnoea (OSA), Dr Susanna SS NG reviewed the pathophysiology of OSA and summarised the major treatment options currently available. The developing concepts of OSA phenotypes and the associated phenotype-based treatments were also introduced.

Genomic medicine and personalised treatment of respiratory diseases is continuously evolving and refining. This will create a paradigm shift and become the standard of care in future diagnosis and treatment of all respiratory diseases. Physicians should keep abreast of the latest developments in precision medicine and apply the research results judiciously in clinical practice to ensure high-quality treatments are tailor-made to the specific needs of the individual patients.

Personalised Care in Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common disease locally and globally and is associated with debilitating symptoms, recurrent exacerbation and early mortality. Since the disease is defined by airflow limitation[1] without specifying underlying abnormal molecular and cellular pathogenetic pathways, it is conceivable COPD is a heterogeneous disease and a common treatment strategy will not fit all. It is thus important to identify clinical phenotypes[2] which are defined as a single or combination of disease attributes or traits that describe different patient subgroups with different response to treatment. This would allow us to implement precision medicine[3] and offer personalised care to patients with this heterogeneous disease.

WHAT ARE THE RELEVANT CLINICAL PHEONTYPES THAT HELP GUIDE PHARMACOTHERAPY

Symptoms & Exacerbation

Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD guidelines[1] classify patients into 4 groups, namely Groups A, B, C and D, according to their severity of symptoms (measured by COPD Assessment Test (CAT) or modified medical Research Council Dyspnea Scale) and frequency of exacerbation and hospitalisation. Though symptoms and exacerbation are strictly not 'clinical phenotypes' but represent severity of disease, their amelioration nevertheless constitutes important goals of treatment[1] and different medications have different impact on symptoms and/or exacerbation. Except for Group A patients who are not too symptomatic (CAT <10) and have infrequent exacerbations, long-acting bronchodilators including long-acting β-agonists (LABAs), long-acting antimuscarinic antagonists (LAMAs) and long-acting β-agonists/inhaled corticosteroid (LABA/ICS) are the drugs of choice for Groups B, C and D patients. Asthma should be excluded when a Group C patient presents with frequent exacerbations in the absence of significant symptoms. Both LABA and LAMA are effective medications in reducing symptoms, improving quality of life and attenuating risk of exacerbation. In one study, indacaterol provided greater symptomatic improvement than tiotropium[4] and may be preferred for symptomatic non-exacerbators. On the other hand, LAMA has consistently been shown to be more efficacious than LABA in preventing exacerbation[5,6] and is recommended as the initial treatment for Groups C and D patients.[1] LABA/LAMA combination is superior to either LABA or LAMA in improving symptoms and protecting patient from exacerbation[7,8] and is the next logical step of treatment when LABA or LAMA alone fails. The effect of LABA/LAMA combination is more pronounced for patients with high baseline symptoms and this class of medication may be the initial treatment for patients whose baseline CAT is greater than 20.[9] Interestingly, in patients with frequent exacerbations (>2 exacerbations in the previous year) or prior hospitalisation due to exacerbation, roflumilast reduced moderate or severe exacerbation compared with placebo in a pre-specified, pooled analysis.[10] This suggests roflumilast is particularly useful for the most severe form of COPD.

Asthma and Chronic Bronchitis

Besides symptoms and exacerbation, the presence of "asthma phenotype' and 'chronic bronchitis phenotype' would help guide the choice of medications. Since both asthma and COPD are common diseases, it is not uncommon to encounter patients with features of both disorders. Asthma-COPD overlap (ACO) has been coined to describe a condition where clinical characteristics of both asthma and COPD are present.[11] A longitudinal cohort study showed that in COPD patients with a codiagnosis of asthma (ASO), use of LABA/ICS was associated with a lower risk of COPD hospitalisation and death compared with the use of LABA alone.[12] Therefore LABA/ICS instead of LABA or LAMA should be prescribed for COPD patients with asthma phenotype. On the other hand, a history of chronic bronchitis (chronic bronchitis phenotype) predicts response to the PDE4 inhibitor roflumilast[13] where the drug reduces moderate to severe exacerbation compared with placebo. Besides reducing exacerbation and improving lung function[14] add-on roflumilast treatment also improves health status from recent prospective, non-interventional studies.[15]

Eosinophilic Phenotype

The overall effect of anti-inflammatory treatment for COPD has been disappointing. However, eosinophilic airway inflammation, which is a hallmark pathology in asthma, has long been recognised in 30-40% of COPD patients.[16] In a group of patients with sputum eosinophilia (eosinophil count ≥3%), use of ICS resulted in improvement in dyspnea and lung function.[16,17] Unfortunately the use of sputum test

to diagnose eosinophilic COPD is cumbersome and requires standardisation. Recently, blood eosinophil count > 162 per uL or 2.6% was found to predict sputum eosinophilia (eosinophil count > 3%) with good sensitivity and specificity.[18] Indeed, peripheral blood eosinophilia predicts reduction in the rate of exacerbation when ICS was added to LABA[19,20,21] or LABA/LAMA,[22] regardless of whether peripheral eosinophil percentage[21,22] or absolute peripheral eosinophil count[19,20] was used. At blood eosinophil count of ≥100 cells/ul, a significant reduction in exacerbation was observed when inhaled budesonide was added to formoterol.[19] The higher the eosinophil count, the greater would be the reduction in exacerbation. At blood eosinophil count of ≥300 cells/ul, almost 50% reduction in rate of exacerbation was recorded when ICS was added to LABA.[19,20] This formed the scientific basis for GOLD COPD 2019 recommendations[1]: ICS can be added to LABA when the blood eosinophil count is ≥100 cells/ul especially if patient has frequent exacerbation (≥2 exacerbations in previous year). The benefit of protecting patient from exacerbation is most profound when the eosinophil count is ≥300 cells/ul, which can be used as the threshold for starting LABA/ICS even if patient has only one exacerbation in the past year. As all these recommendations were based on post-hoc or pre-specified analyses of previous trials, further studies are needed to confirm the validity of the proposed pathways. Eosinophilic phenotype is also associated with clinical benefits from the use of roflumilast. In a pooled analysis,[10] the reduction in exacerbation after use of roflumilast is more pronounced the higher the baseline blood eosinophil count (19% reduction when the eosinophil count is ≥150 cells/ul and 23% reduction when eosinophil count is ≥300 cells/ul). In patients with prior hospitalisation, the reduction is even more significant (34% reduction when eosinophil count is ≥150 cells/ul and 43% reduction when eosinophil count is ≥300 cells/ul). This correlation can be explained by a recent study[23] which reported that the use of roflumilast was associated with a significant reduction in eosinophils in bronchial biopsy samples compared with placebo, suggesting that the eosinophil is the target of the anti-inflammatory and clinical effects of roflumilast. Mepolizumb, a monoclonal antibody against IL-5, also decreased the rate of moderate or severe exacerbation than placebo in those with eosinophilic phenotype.[24] During exacerbation, patients with a blood eosinophil count of >2% had a higher treatment failure rate (66%) if prednisolone treatment was not given and a low failure rate (11%) if they received the drug.[25] All in all, eosinophilic phenotype represents a group of patients who are responsive to anti-inflammatory treatment (ICS and Roflumilast).

LABA/LAMA, LABA/ICS, TRIPLE AND OTHER MAINTENANCE THERAPIES

When a patient continues to exacerbate despite a LABA or LAMA, the question will be whether subsequent treatment should be escalated to LABA/LAMA or LABA/ICS. The result of the FLAME Trial[26] has demonstrated categorically a LABA/LAMA (Indacaterol-glycopyrronium) was more efficacious than a LABA/ICS (salmeterol-fluticasone) in preventing COPD exacerbations in patients with a history of exacerbation in the past year irrespective of the baseline eosinophil count.[27] However, the result of the IMPACT Trial was the direct opposite: LABA/ICS (fluticasone furorate-vilanterol) was superior to LABA/LAMA (umeclidinium-vilanterol) in reducing moderate or severe exacerbation.[28] These contradicting results may be due to differences in patient selection and methodology used. Patients with history of asthma were not excluded in the IMPACT Trial and ≥70% of their patients had ≥2 moderate or ≥1 severe exacerbations in the previous year, suggesting they are a sicker group of patients. Patients assigned to LABA/LAMA group in the IMPACT Trial would have had their ICS stopped abruptly, which may have led to exacerbation. Attending physicians should balance the risk-benefit of LABA/LAMA vs LABA/ICS before prescribing, bearing in mind the side effects of ICS and whether the patient has the eosinophilic or asthmatic phenotype that favors the use of ICS. When the patient continues to exacerbate despite LABA/LAMA or LABA/ICS, triple therapy should be prescribed in an effort to cut the rate of exacerbation.[22,28] For the most frequent exacerbators, roflumilast can be considered to be added to maintenance inhalation treatment,[10] particularly if the patient has the eosinophilic phenotype. Azithromycin given for one year also reduces risk of exacerbation but is associated with the potential side effects of prolongation of QT interval, hearing impairment and an increased incidence of bacterial resistance.[29]

SIDE EFFECTS OF ICS AND DE-ESCALATION

ICS is one of most widely prescribed medications for COPD patients and carries a range of adverse effects including pneumonia, tuberculosis and non-tuberculous mycobacterial infection, osteoporosis and bone fracture, cataract and the local side effect of oropharyngeal candidiasis.[30] The risk of pneumonia increases with daily dose and duration of ICS treatment.[31] Unfortunately, ICS is over-prescribed and evidence-based treatment recommendation is not followed. In a retrospective analysis of a US cohort, 25% of COPD patients progressed to triple therapy within 12 months of initiating treatment with monotherapy or dual therapy. Exacerbations were reported in only 50% of these patients.[32] With the availability of effective medications like LABA/LAMA combination, every effort should be made to withdraw ICS from patients when it is not effective, not indicated or when unacceptable adverse effects are encountered. The SUNSET study[33] has demonstrated that for infrequent exacerbators (≤1 exacerbation in the previous year) with eosinophil count <300 cells/ul, triple therapy can be de-escalated to indacaterol/glycopyrronium without any increase in exacerbation.

It is interesting to note from recent studies[20,22] that the use of extra fine formulation of inhaled beclomethasone was not associated with increased risk of pneumonia. Further studies are required to confirm the benignity of this ICS preparation.

CLINICAL PHENOTYPES THAT HELP GUIDE BRONCHOSCOPIC LUNG VOLUME REDUCTION

Though lung volume reduction surgery (LVRS) improves health status and lung function compared with medical care,[34] it is an invasive surgery associated with significant morbidities. The last decade saw the emergence of bronchoscopic lung volume reduction (BLVR) techniques to treat severe emphysema with hyperinflation. The insertion of one-way endobronchial value (EBV) is widely practiced and the treatment outcomes look promising. Since the goal of EBV treatment is to achieve lobar atelectasis, responsive patients should have a lack of collateral ventilation to the target lobe and a complete fissure on CT scan.[36] EBV treatment for patient with this specific phenotype would increase their FEV_1 and 6 minutes walking distance.[35,36]

CONCLUSION

Several clinical phenotypes of COPD have been found to be helpful to guide pharmacotherapy and non-pharmacotherapy. It is hoped further 'treatable traits' can be discovered to help us provide more personalised care to individual patient.

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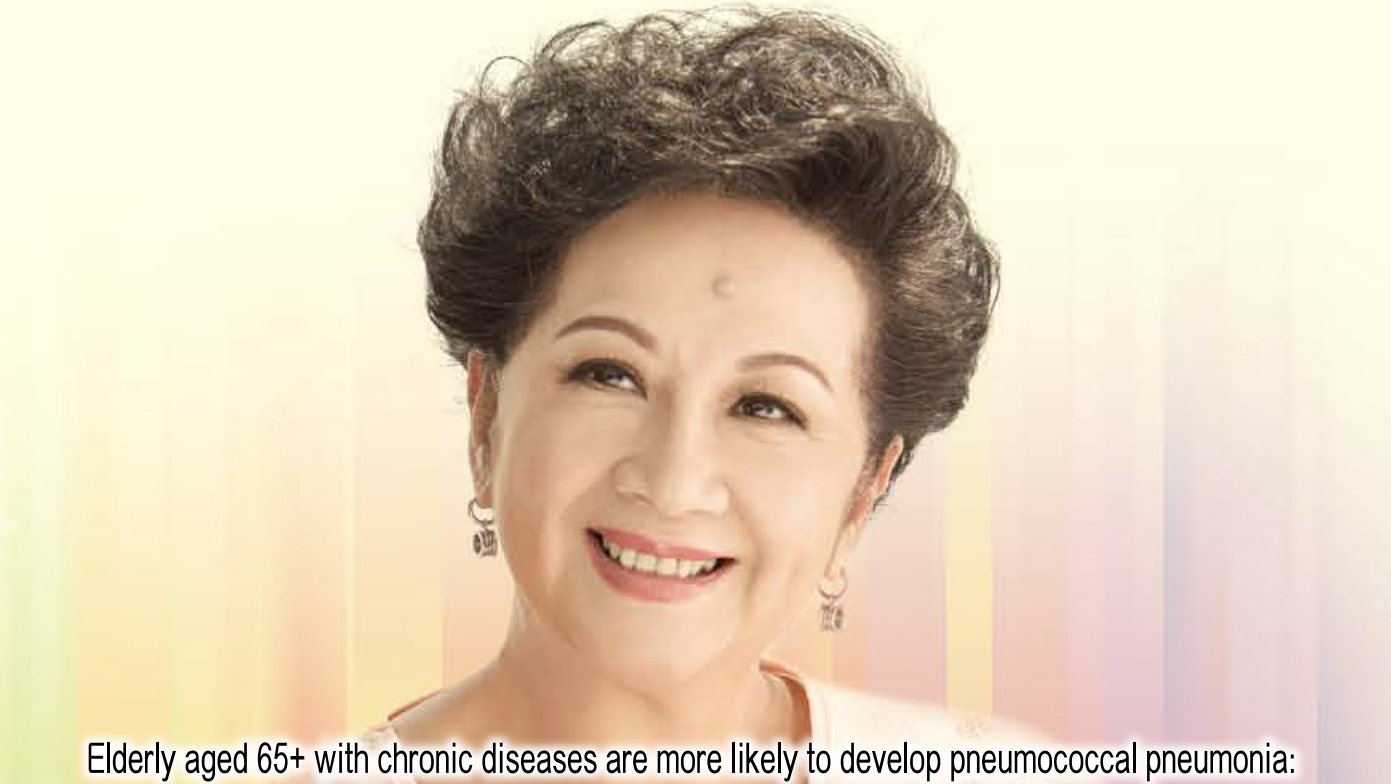

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CHRONIC CVD†

3.8 folds[1]

CHRONIC LUNG DISEASE

7.7 folds[1]

* Compared with healthy individuals aged 65 or above
* Conjugate vaccine induces immune memory and provides long-term protection[3,4]
† Chronic cardiovascular disease

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Management of Severe Asthma in Adults

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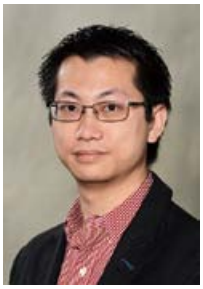


Dr Ka-pang CHAN Dr Fanny WS KO

INTRODUCTION

For the management of asthma, it is essential to differentiate between difficult-to-treat asthma and severe asthma as the approach to treatment would be different. Asthma is considered difficult-to-treat if it remains uncontrolled despite Global Initiative for Asthma (GINA) step 4 or 5 treatment (e.g. medium or high dose inhaled corticosteroids [ICS] plus a second controller), or asthma which requires such treatment to maintain good symptom control and reduce the risk of exacerbation.[1] Various modifiable factors may contribute to difficult-to-treat asthma, including incorrect inhaler technique, suboptimal medication adherence, associated comorbid conditions and even wrong diagnosis. Severe asthma is considered a subset of difficult-to-treat asthma after exclusion of the modifiable factors other than poorly controlled asthma itself. It is defined as asthma that is uncontrolled despite adherence to maximal optimised therapy and despite having fully addressed modifiable factors; severe asthma is also defined as asthma that worsens when high dose treatment is decreased.[1]

Severe asthma is not common but casts a considerable burden on the healthcare system and patients. According to a Dutch survey which included adult asthma patients, 17.4% and 3.6% of them had difficult-to-treat asthma and severe asthma respectively.[2] Although severe asthma involves only a small proportion of the asthma population, it generates a huge amount of asthma-related healthcare expenditure.[3] An observational cohort by a French study group found that 83% of patients with severe asthma experienced at least one exacerbation and 14% were hospitalised for asthma over the previous 12 months.[4] Furthermore, patients with severe asthma experienced more severe symptoms, with higher functional and psychological limitation than the general asthma population.[5]

WHAT DO YOU NEED TO DO FOR PATIENTS WITH DIFFICULT-TO-TREAT ASTHMA?

Optimise Asthma Management

Differentiation between difficult-to-treat asthma and severe asthma is crucial before adding on potentially expensive and unnecessary treatments. This can be done by looking for factors contributing to symptoms and exacerbations.[1] A number of modifiable patient factors should be optimised before diagnosing severe asthma, and they are listed in Table 1.[1,6] Among these factors, incorrect inhaler technique and suboptimal medication adherence are most common in daily practice, and they should be reviewed at every clinic visit. Timely influenza vaccination, self-management plan and asthma education should be reinforced.

Table 1. Modifiable risk factors for difficult-to-control asthma (modified from reference 1)

Incorrect inhaler technique
Suboptimal medication adherence
Ongoing exposure to triggering factors (e.g. smoking, environmental agents, drugs)
Overuse of short-acting beta-agonists
Medication side effects
Anxiety, depression and social difficulties
Asthma-related comorbidities

Review the Diagnosis and Treat the Comorbid Conditions

Several asthma mimics have been described (e.g. COPD, bronchiectasis, vocal cord dysfunction) and a diagnosis of asthma based on symptomatology only has been proven to be inaccurate.[7] If the initial diagnosis of asthma is doubtful, it is worthwhile to revisit the diagnosis by some confirmatory tests, for example, reversibility on spirometry, diurnal variation of peak flow rate and bronchial challenge test. Coexisting comorbid conditions such as rhinosinusitis, gastroesophageal reflux disease, obesity, obstructive sleep apnea, depression, anxiety should be well managed as they can also contribute to the difficult-to-treat status.[1,6] Indeed, the above considerations should be reviewed regularly at each follow-up, especially when there is worsening of asthma control.

Non-biologic Add-on Therapy

If asthma remains uncontrolled on a moderate dose of ICS, a trial of high dose ICS or combination with long-acting beta-agonist (LABA) should be considered. The GINA guideline also recommends other add-on therapies before upgrading the treatment to more expensive biologics.

Long-acting muscarinic antagonist

Tiotropium, a long-acting muscarinic antagonist (LAMA), works by relaxing the airway smooth muscle and thus reduces bronchospasm. The use of tiotropium

soft-mist inhaler contributes to improving lung function, lengthening the time to first exacerbation, and reducing the risk of severe exacerbation by 21%.[8] LAMAs other than tiotropium may work in severe asthma, but the evidence is lacking.

Leukotriene receptor antagonist

Leukotriene receptor antagonist (LTRA) is used as an add-on treatment for uncontrolled moderate asthma while on moderate to high dose ICS. It is beneficial for reducing moderate and severe asthma exacerbations, improving lung function and asthma control in patients with suboptimal asthma control even with ICS.[9] Current data show that LTRA is beneficial to patients with clear evidence of aspirin sensitivity[10], but not in unselected patients with severe asthma.[11]

Oral corticosteroids

Oral corticosteroids (OCS) were once the standard treatment for patients with severe asthma when biologics were not available. Nowadays, 26.8% severe asthma patients still take maintenance OCS.[12] Eosinophilic asthma is more responsive to OCS than non-eosinophilic asthma. In contrast to the conventional practice of titrating OCS according to clinical features, a recent meta-analysis showed that titration of OCS based on sputum eosinophil counts could result in more reductions in exacerbation rates.[14] Furthermore, keeping a blood eosinophil count of < 0.2 x 109/L by OCS can lead to a decrease in asthma exacerbations and better symptom control.[14] However, the use of OCS is limited by various acute and chronic adverse effects.[15] Physicians should try to use the lowest dose of OCS for the desired therapeutic effect.

For those patients with uncontrolled asthma despite conventional and add-on treatment, the next step is biologics treatment based on disease phenotype. Ineffective add-on treatment should be discontinued.

HOW TO PHENOTYPE SEVERE ASTHMA?

Disease phenotyping has revolutionised the management of asthma from stepwise treatment to phenotype-based treatment. As asthma is a clinical syndrome comprising of a broad spectrum of symptoms, different molecular pathways may be involved. Most of these pathways are associated with evidence of cellular inflammation in the airway.[16] Identifying treatable traits may potentially guide the choice of and predict the outcome of treatment. For example, blood or airway eosinophilia is usually a good indicator of corticosteroid responsiveness.[13,14] The process of characterising observable treatable traits is termed phenotyping, which allows physicians to select the most appropriate add-on therapies for patients with severe asthma. Phenotype identification is usually performed in patients on high dose ICS, as most clinical trials on add-on or biologic treatments were performed in this group of patients.

Among the various inflammatory phenotypes, Type 2 inflammation is the most important one, and its mechanism forms the basis of several biologic treatments. This inflammation pathway is characterised by the presence of interleukin (IL)-4, IL-5 and IL-13. IL-4 and IL-5 promote the production of immunoglobulin E (IgE) and eosinophils respectively, leading to the occurrence of eosinophilic inflammation and atopic phenomenon in asthma.[1,6] Sputum eosinophils, blood eosinophils, fractional exhaled nitric oxide (FeNO) and serum periostin are clinical biomarkers to diagnose Type 2 inflammation and predict treatment responses (Table 2). Type 2 inflammatory mechanism is also implicated in some diseases including aspirin-exacerbated respiratory disease, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis and atopic dermatitis. On the contrary, non-Type 2 inflammation is poorly characterised, and it includes neutrophilic and pauci-granulocytic subtypes.

Table 2. Clinical features that predict Type 2 inflammation (modified from reference 1)

Type 2 inflammation if any of the following are found while the patient is on ICS[1]
1. Blood eosinophils ≥ 0.15 x 10^9/L and/or
2. FeNO ≥ 20 ppb and/or
3. Sputum eosinophils ≥ 2%, and/or
4. Asthma is clinically allergen-driven

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids

PHENOTYPE-BASED TREATMENT

Five biologics have been approved by the US Food and Drug Administration (FDA) for antagonising the Type 2 inflammatory mechanisms in severe asthma. In general, severe asthma patients with clinical and laboratory features manifesting Type 2 inflammation (e.g. allergen-driven, high IgE level, high eosinophil activity) and exacerbations are good candidates for such treatment.

Omalizumab, a monoclonal antibody targeting at the high-affinity receptor binding site on human immunoglobulin (Ig) E, is the first approved biologic treatment available for severe allergic asthma. This treatment can be considered in severe asthma patients with a total IgE level between 30 and 700 IU/mL in the United States (30 to 1500 IU/mL in Europe), and documented sensitisation to a perennial aeroallergen by positive skin testing or by in vitro-specific serum IgE testing. There are also upper limits of body weight beyond which administration is not recommended. The clinical response is independent of the baseline IgE level. Several real-life studies have confirmed the post-marketing clinical efficacy of omalizumab. A study by a Belgian group showed that omalizumab could effectively reduce exacerbation rate by 65% and improve quality of life (QOL) of the patients in 52 weeks. In the same study, 57% of the treated patients had either completely discontinued or reduced dose of OCS therapy.[16] Two studies found a more significant reduction in exacerbations was observed if blood eosinophil level was ≥ 0.26 – 0.30 x 109/L.[17,18] However, this was not confirmed in a subsequent observational trial employing a cutoff of ≥ 0.3 x 109/L.[19] Therefore, whether a higher level of blood eosinophils can be translated into a better response to omalizumab is still debatable. An Italian study confirmed that the treatment response of omalizumab remained stable for over 60 months. Long-term omalizumab use may give a higher chance of stepping down add-on therapies and

lowering the dose of OCS.[20]

Three different biologics work on the IL-5 pathway, mepolizumab, reslizumab and benralizumab. The anti-IL-5s (mepolizumab and reslizumab) bind circulating IL-5, while anti-IL5 receptor α (benralizumab) binds to IL-5 receptor alpha subunit leading to lysis of eosinophils. There is evidence showing a significant reduction in asthma exacerbation of ~ 55% by using these three biologics.[21] They also have beneficial effects on lung function, symptom control and QOL.[21] Among the three, both mepolizumab and reslizumab have been shown to have an OCS-sparing effect.[22,23] Inter-study comparisons revealed no difference between mepolizumab and reslizumab in their efficacies or safety measures.[24] Although benralizumab can induce direct and nearly complete depletion of eosinophils, which is theoretically better than simply targeting the IL-5 molecule,[25] there are however no head-to-head trials comparing the efficacy among these biologic agents. Blood eosinophil level eligible criterion for anti-IL-5 therapies differs among different regulatory authorities and countries and previous data have shown a better response in the context of a higher baseline blood eosinophil level. [26]

Dupilumab, a fully human anti-IL-4 receptor α monoclonal antibody that blocks both IL-4 and IL-13 signalling, has been approved by the US FDA in October 2018 for treatment of moderate-to-severe asthma. Two recent phase 3 trials showed that dupilumab could halve the annual exacerbation rate, improve lung function and asthma control in unselected patients with moderate-to-severe asthma, and those with corticosteroid-dependent severe asthma.[27,28] These treatment effects are more pronounced in those with raised baseline levels of blood eosinophils and FeNO.[27,28] Also, dupilumab treatment allows a 70% reduction of OCS dose in corticosteroid-dependent severe asthma, and 80% of patients had a dose reduction of at least 50%.[28] Although clinical trials of dupilumab for atopic dermatitis have reported an increase in the incidence of conjunctivitis in patients who received dupilumab,[29] there was no significant increase in the incidence of conjunctivitis in asthma patients after using it.[27,28]

The eligible criteria and predictors of good response for the above biologics are summarised in Table 3.

The duration of biologic treatment depends on the clinical response. A trial duration of at least four months is recommended to judge the effectiveness.[1] Once a good response is confirmed, the biologic treatment should be continued as long as possible, and at the same time effort should be put to reduce the dose of other maintenance treatment especially OCS. A moderate dose of ICS should be kept at least as the baseline for control.[1] A trial of biologics withdrawal may be considered after at least 12 months of treatment if asthma remains well controlled on medium dose ICS.[1] However, in a follow-up analysis after the completion of a drug trial, patients who had mepolizumab ceased had an increased risk of exacerbation similar to baseline, which was preceded by a rise in sputum and blood eosinophil level.[30] While in an observational trial for omalizumab, there was no increase exacerbation rate after cessation of omalizumab despite a rising of IgE level.[31] Evidence is still lacking regarding the timing to cease the use of biologics. Careful monitoring should be exercised, and detailed discussion with the patients should be done when planning for the withdrawal of biologics. In contrary, when there is no significant response detected after initiation of a biologic, another biologic may be tried. Ineffective add-on treatment should be ceased to avoid polypharmacy. At the same time, general asthma care including patient education, regular review of inhaler technique and drug compliance should be performed regularly.

Although helminth infection is uncommon in Hong Kong, this diagnosis should be considered in asthma patients with peripheral eosinophilia. The effect of biologics on patients with suspected helminth infection is unknown, as patients with such infection were excluded from participation in clinical studies.

Patients with severe asthma should not be labelled merely as non-Type 2 if there is a lack of such evidence in a stable state. Blood eosinophil and FeNO can be checked up to 3 times to look for such features, especially during the worsening of asthma and before prescribing OCS.[1] Biologics treatment is not useful in non-Type 2 patients. A trial of add-on treatment including tiotropium, LTRA and OCS may be tried in this type of patients. If asthma remains uncontrolled despite all these measures, bronchial thermoplasty may be considered, but the patients should be enrolled into a registry for future audit purpose. However, data on its

Table 3. Eligible criteria and predictors of good response for the four biologic treatments (summarized from references 1, 17-19, 22-28, 33-37)

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab
	Anti-IgE	Anti-IL-5	Anti-IL-5	Anti-IL-5 receptor α	Anti-IL-4 receptor α
Eligible criteria*	**Severe allergic asthma** Sensitisation to inhaled allergen(s) on skin prick testing or specific IgE Total serum IgE level and BW within dosing range More than a specific number of exacerbations within last year	Blood eosinophil ≥ 0.15 x 10^9/L	**Severe eosinophilic asthma** Exacerbations in last year Blood eosinophil ≥ 0.4 x 10^9/L	Blood eosinophil≥ 0.3 x 10^9/L	Blood eosinophil ≥ 0.15 x 10^9/L FeNO ≥ 25 – 50 ppb
Predictors of good response	FeNO ≥ 20 ppb Allergen-driven symptoms Childhood-onset asthma Blood eosinophils ≥ 0.26 – 0.30 x 10^9/L‡	Higher blood eosinophils More exacerbations in previous year Adult-onset of asthma Nasal polyposis			Higher blood eosinophils Higher FeNO
Injection schedule	Every 2-4 weeks, SC injection	Every 4 weeks SC injection	Every 4 weeks IV infusion	Every 4 weeks for 3 doses then every 8 weeks SC injection	Every 2 weeks SC injection
Dose	Based on BW and baseline IgE level	100mg	3mg/kg	30mg	Loading 400mg then 200mg Loading 600mg then 300 mg (also for those on OCS)
Side effects	Injection site reactions, anaphylaxis (~0.2%)	Injection site reaction, anaphylaxis is rare Drug-specific: herpes zoster (mepolizumab), transient increase in CPK (reslizumab) , headache (benralizumab), transient eosinophilia (dupilumab)			

BW: body weight; CPK: creatine phosphokinase; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; IL: interleukin; IV: intravenous; OCS: oral corticosteroid; ppb: parts per billion; SC: subcutaneous

** local eligibility criteria may apply ‡ Not a universal observation (see inner text)*

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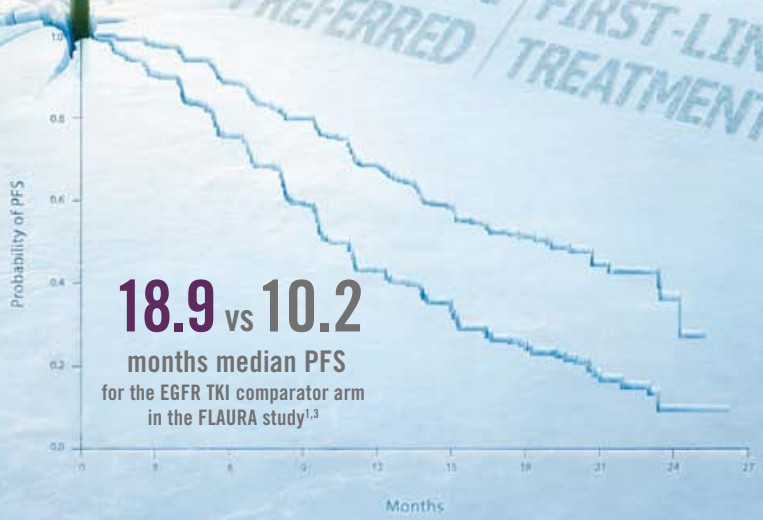

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Study design[3]: This was a double-blind, phase 3 trial, with 556 patients with previously untreated, EGFR mutation–positive (exon 19 deletion or L858R) advanced NSCLC randomly assigned in a 1:1 ratio to receive either osimertinib (at a dose of 80 mg once daily) or a standard EGFR-TKI (gefitinib at a dose of 250 mg once daily or erlotinib at a dose of 150 mg once daily). The primary end point was investigator-assessed progression-free survival.

EGFR=epidermal growth factor receptor. EGFRm=epidermal growth factor receptor mutation. PFS=progression-free survival. NCCN=National Comprehensive Cancer Network. NSCLC=non-small cell lung cancer. TKI=tyrosine kinase inhibitor.

References: 1. TAGRISSO™ Hong Kong Prescribing Information. Nov 2018. **2.** Non-Small Cell Lung Cancer NCCN Evidence BlocksTM (Version 2.2019). Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed: 29 Nov 2018. **3.** Soria JC, et al; FLAURA Investigators. N Engl J Med 2018;378:113-125.

Presentation: 80 mg and 40 mg osimertinib tablet (as mesylate). **Indications:** 1. First-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (*EGFR*) mutations; 2. Treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. **Dosage:** 80mg once daily with or without food. Swallowed whole with water, or dispersed in non-carbonated water and immediately swallowed or administered through nasogastric tube. Dose reduction may be required based on individual safety and tolerability. **Contraindications:** Hypersensitivity to the active substance or excipients; concomitant use of St. John's Wort. **Precautions:** A validated test should be performed to determine *EGFR* mutation status. Caution in patients with severe or end-stage renal impairment; cardiac risk factors or those with conditions that can affect left ventricular ejection fraction; develop relevant cardiac signs/symptoms; presenting with signs and symptoms suggestive of keratitis; greater 65 years of age; body weight less than 50 kg; pregnancy; lactation. Not recommended in severe hepatic impairment. Discontinue permanently if patients develop interstitial lung disease (ILD); develop QTc interval prolongation in combination with: Torsade de pointes, polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. **Interactions:** Strong CYP3A inducers, moderate CYP3A4 inducers, rosuvastatin, fexofenadine. **Undesirable effects:** Dry skin; rash; pruritus; paronychia; leukocytes, lymphocytes, neutrophils, platelet count decreased; diarrhoea; ILD; stomatitis. **Full local prescribing information is available upon request. API.HK.TAG.1118**
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long-term safety is still limited at this stage.[1]

MANAGEMENT OF COMORBID CONDITIONS AND MAINTAING THE QUALITY OF LIFE

A holistic approach to tackle related comorbid conditions and maintain patient's QOL should be adopted when managing a patient with asthma. Comorbidities are common among asthma patients and may complicate the asthma control. These conditions should be sorted proactively and treated adequately.[32] Common asthma-associated comorbidities are listed in Table 4. Non-pharmacological interventions including asthma education, self-management program, psychological therapies and lifestyle modification are important strategies not to be omitted.

Table 4. Common asthma-associated comorbidities (modified from reference 31)

Airway-related comorbid conditions	Airway-unrelated comorbid conditions
Allergic rhinitis	Gastro-oesophageal reflux disease
Chronic rhinosinusitis ± nasal polyposis	Obesity
Vocal cord dysfunction	Obstructive sleep apnoea
Dysfunctional breathing	Anxiety and depression
Allergic bronchopulmonary aspergillosis / severe asthma with fungal sensitisation	
Bronchiectasis	
Chronic obstructive pulmonary disease	

CONCLUSION

Severe asthma casts a considerable burden on the healthcare system and patients. The exciting advances in the understanding of its molecular pathophysiology have opened a new door of personalised and phenotype-based treatment. Before initiation of add-on treatment for difficult-to-control asthma, it is desirable to ensure optimisation of modifiable factors and exclusion of alternative diagnoses. Personalised management of comorbid conditions and interventions aimed at improving QOL would help to improve outcomes for patients with severe asthma.

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Maximum recommended dose is 450 mg taken orally once daily with food. • Temporary dose interruption and/or dose reduction of Zykadia therapy may be required based on individual safety and tolerability. • Zykadia should be discontinued in patients unable to tolerate 150 mg taken once daily with food. **Children (below the age of 18 years):** The safety and efficacy of Zykadia have not been established in pediatric patients. **Special populations:** • No dose adjustment necessary in patients with mild to moderate renal impairment. Use caution in patients with severe renal impairment. • No dose adjustment necessary in patients with mild hepatic impairment. • Not recommended in patients with moderate to severe hepatic impairment. • The limited data on the safety and efficacy of ceritinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients. There are no available data on patients over 85 years of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients of Zykadia. **Warnings and precautions:** • **Hepatotoxicity:** Monitor with liver laboratory tests prior to the start of treatment every 2 weeks during the first three months of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated. • **Interstitial lung disease (ILD) / Pneumonitis:** Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Zykadia in patients diagnosed with any-grade treatment-related ILD/pneumonitis. • **QT interval prolongation:** Avoid use of Zykadia in patients with congenital long QT syndrome. Periodic monitoring with electrocardiograms (ECGs) and periodic monitoring of electrolytes (e.g., potassium) is recommended in patients with pre-existing bradycardia (heart rate less than 60 beats per minute [bpm]), patients who have a history of or predisposition for QTc prolongation, patients who are taking anti-arrhythmics or other medicinal products that are known to prolong the QT interval and patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. In case of vomiting, diarrhea, dehydration, or impaired renal function, correct electrolytes as clinically indicated. Permanently discontinue Zykadia in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold Zykadia in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate Zykadia by reducing dose by 150 mg. • **Bradycardia:** Avoid use of Zykadia in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia if necessary. Permanently discontinue Zykadia for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, reinitiate Zykadia by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring. • **Gastrointestinal adverse reactions:** No patients required dose reduction or discontinuation of Zykadia due to diarrhoea, nausea or vomiting. Monitor and manage patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as clinically indicated. Dose interruption and dose reduction should be employed as necessary. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose. • **Hyperglycemia:** Monitor fasting serum glucose prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. • **Elevations of lipase and/or amylase:** Monitor lipase and amylase prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. **Pregnancy, lactation, females and males of reproductive potential: Pregnancy:** Should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib. **Lactation:** A decision should be made whether to discontinue breast-feeding or discontinue/abstain from Zykadia taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **Females of reproductive potential:** Females of reproductive potential to be advised to use a highly effective method of contraception while taking Zykadia and for up to 3 months after discontinuation. **Infertility:** The potential for Zykadia to cause infertility in male and female patients is unknown. **Adverse drug reactions: Very common (≥10%):** Liver laboratory test abnormalities, diarrhoea, fatigue, abdominal pain, nausea, decreased appetite, vomiting, weight decreased, constipation, blood creatinine increased, rash, anaemia, and oesophageal disorder. **Common (≥1 to <10%):** Electrocardiogram QT prolonged, hyperglycaemia, amylase increased, vision disorder, pericarditis, hypophosphataemia, lipase increased, bradycardia, abnormal liver function tests, pneumonitis, renal failure, hepatotoxicity, and renal impairment. **Uncommon (≥0.1 to <1%):** Pancreatitis. **Interactions:** • **Strong CYP3A inhibitors:** Avoid concurrent use of strong CYP3A inhibitors. If concomitant use of strong CYP3A inhibitors is unavoidable, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone, reduce the Zykadia dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the Zykadia dose that was taken prior to initiating the strong CYP3A inhibitor. • **P-gp inhibitors:** Exercise caution with concomitant use of P-gp inhibitors and carefully monitor adverse drug reactions. • **Strong CYP3A and P-gp inducers:** Avoid concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort (*Hypericum perforatum*). Exercise caution with concomitant use of P-gp inducers. • **Agents that affect gastric pH:** Caution is advised with concomitant use of proton pump inhibitors, as exposure of ceritinib may be reduced. • **CYP3A and CYP2C9 substrates:** Avoid co-administration of Zykadia with CYP3A substrates known to have narrow therapeutic indices (e.g., astemizole, cisapride, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus) and CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin). • **CYP2A6 and CYP2E1 substrates:** Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions. • **Agents that are substrates of transporters:** Caution should be exercised with concomitant use of BCRP substrates (e.g. rosuvastatin, topotecan, sulfasalazine) and P-gp substrates (digoxin, dabigatran, colchicine, pravastatin) and ADRs carefully monitored. • **Drug-food/drink interactions:** Zykadia should be taken with food. For patients who develop a concurrent medical condition and are unable to take Zykadia with food, Zykadia can be taken on an empty stomach as the alternate continued treatment regimen, in which no food should be eaten for at least two hours before and one hour after the dose. Patients should not alternate between fasted and fed dosing. Dose must be adjusted properly. Patients should be instructed to avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and increase the bioavailability of ceritinib. **Packs and prices:** 150 mg (50's, 3 x 50's), not all pack size are marketed. **Legal classification:** P1S1S3 **Reference:** EU APR 2018, including 0920s (ASCEND-8)

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Precision Medicine in Lung Cancer

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2019.

INTRODUCTION

Over the past decade, there has been enormous development in the diagnostics and therapeutics in lung cancer, particularly in the management of advanced stage non-small cell lung cancer (NSCLC). These developments have revolutionised the management paradigm. Choosing the most appropriate treatment option for the patient, focusing not only on the pathology but also patients' characteristics cannot be over emphasised in the current standard of practice.

MOLECULAR DIAGNOSTICS FOR ADVANCED STAGE LUNG CANCER

Nowadays, testing for driver mutations in patients with advanced NSCLC has been incorporated into the standard of care. According to the guidelines from the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC) and the Association of Molecular Pathologists (AMP), analysis of either the primary tumor or of a metastasis for epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) for all patients whose tumor contains an element of adenocarcinoma, regardless of the clinical or demographic characteristics of the patients, are recommended. There are, however, more and more molecular tests that have become available now and the investigation panel can be extended to include *ROS1* rearrangement or its expression, *BRAF* mutation as well as programmed death ligand 1 (PD-L1) expression.

The most common method for testing *EGFR* mutation is by polymerase chain reaction (PCR)-based tests on tumor tissue. However, adequate amount of tumor cells has to be present in the specimen for optimal PCR test sensitivity and it often requires invasive procedures to obtain tumor tissue. In recent years, liquid biopsies, i.e. blood-based tests, have been used to detect mutations in cell-free circulating tumor DNA (ctDNA). This has emerged as an alternative way to detect *EGFR* mutation by a non-invasive method. The advantage of liquid biopsy is that it is non-invasive; turnover time is as short as one day; multiple testing is technically feasible, with a sensitivity of 60 to 80%[1,2]. Liquid biopsy is now recommended by IASLC to identify *EGFR* mutations if tissue is limited and/or insufficient for molecular testing.

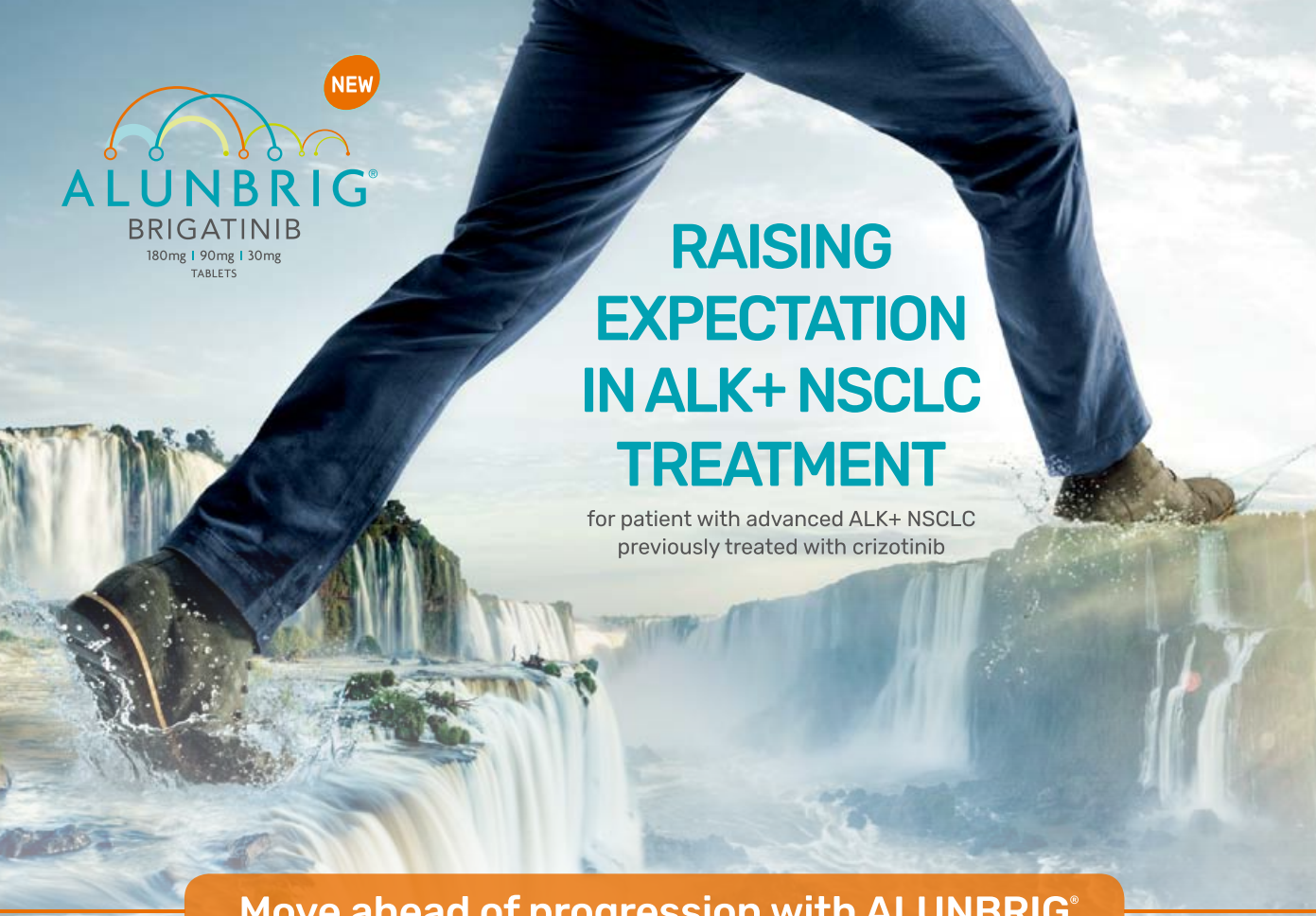
Next-generation sequencing (NGS) is another major development in cancer diagnostics in recent years. NGS is a type of DNA sequencing technology that involves parallel sequencing of multiple small fragments of DNA. NGS can sequence whole genome in a single test and provide a comprehensive mutational landscape of tumors. Studies with NGS also suggested that lung cancer has high level of genetic complexity with different mutation burden among the different histological types. The patterns of genetic mutations are also different between smokers and non-smokers. From the research point of view, NGS opens new avenues toward understanding cancer development and allows for identification of potential therapeutic targets for personalised therapy in NSCLC. In advanced NSCLC, NGS may also allow identification of novel targetable mutations, detection of rare mutations and prediction of emergence of drug resistance. As it has very high resolution, NGS can also overcome some of the technical problems with conventional molecular tests, namely false negative results from inadequate tumor cells and fragmented or cross-linked DNA for tests performed on formalin-fixed paraffin-embedded tumors. NGS is now commercially available and can be performed on tumor tissue as well as blood samples. The high costs of NGS, however, remain a hurdle to wider application especially in the public healthcare setting with limited resources[3].

THERAPEUTICS FOR ADVANCED STAGE LUNG CANCER

The development of targeted therapy and immunotherapy for advanced NSCLC has led to significant changes in the treatment paradigm. For patients with druggable targets, targeted therapy has replaced systemic chemotherapy as upfront first line treatment for advanced stage NSCLC. Targeted therapy for disease progression after first line tyrosine kinase inhibitors have also been developed and allow patients to receive more tolerable treatment with improved survival.

EGFR Mutant NSCLC

There are currently at least four epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKI) available in Hong Kong, with three being mainly used



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A Robust Response[1#]

56% ORR[a]
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Associated with longer PFS vs ceritinib/alectinib in MAIC[3*]

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CI=confidence interval; CNS=central nervous system; IRC=Independent Review Committee; NE=not estimable; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival. [a]Investigator assessed. [b]IRC assessed. [c]In patients with any brain metastases at baseline. [d]Among patients with measurable brain metastases (≥10 mm in longest diameter) at baseline. * MAIC=in a matching-adjusted indirect comparison which conducted to estimate the relative efficacy of these agents in the crizotinib-refractory setting. #180mg once daily with 7-day lead-in at 90mg once daily.

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Reference: **1.** Alunbrig SmPC updated 18 Jan 2019 http://www.medicines.org.uk/emc/product/9691/smpc accessed 20 Jan 2019 **2.** Ahn M et al., WCLC ALTA slides. Oral Presentation IASLC WCLC, 2017 (Abstract 8027) **3.**Reckamp K et al., Curr Med Res Opin 2018 (http://doi.org/10.1080/03007995.2018.1520696) **4.**Alunbrig HK prescribing information (PLFT0156A1)

Abbreviated product information:
C: Brigatinib I: Patients w/ anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. **D:** Initially 90 mg once daily for the 1st 7 days, increased to 180 mg once daily if initial dose is tolerated. **SP:** Risk of interstitial lung disease (ILD)/pneumonitis; HTN; bradycardia; visual disturbances (eg, blurred vision, diplopia, & reduced visual acuity); creatine phosphokinase (CPK) & pancreatic enzyme elevation; hyperglycemia. Withhold treatment in patients w/ Grade 3 or 4 CPK elevation; Grade 3 or 4 pancreatic enzyme elevation; inadequate hyperglycemic control. Discontinue in case of Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis; Grade 4 HTN or recurrence of Grade 3 HTN; life-threatening bradycardia; Grade 4 visual disturbances. Use w/ caution in combination w/ antihypertensive agents causing bradycardia. Females of reproductive potential should use effective non-hormonal contraception during treatment & for at least 4 mth following the final dose. Males w/ female partners of reproductive potential should use effective contraception during treatment & for at least 3 mth after last dose. Pregnancy & lactation. Children. **AR:** Pneumonia, ILD/pneumonitis; increased CPK. Nausea, diarrhea, vomiting, constipation, abdominal pain; fatigue, pyrexia; cough, dyspnea, hypoxia; headache, peripheral neuropathy; rash; HTN; muscle spasms, back pain, myalgia, arthralgia, pain in extremity; decreased appetite; visual disturbance; insomnia; increased AST, lipase, ALT, amylase, alkaline phosphatase; hyperglycemia, decreased phosphorus, prolonged activated partial thromboplastin time; anemia, lymphopenia. **INT:** Increased plasma conc & adverse reactions w/ strong CYP3A inhibitors [eg, certain antivirals (boceprevir, cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (clarithromycin), antifungals (itraconazole, ketoconazole, posaconazole, voriconazole), conivaptan]; grapefruit or grapefruit juice. Decreased plasma conc & efficacy w/ strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort). Decreased conc & loss of efficacy of CYP3A substrates (eg, hormonal contraceptives).

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in first line setting and a third generation EGFR-TKI which can be used in both first and second line setting. Choosing the appropriate EGFR-TKI not only relies on the EGFR mutation status, but also on patient's performance status.

Exon 19 deletion and L858R mutation in exon 21 are the two most common sensitising *EGFR* mutations. For advanced stage NSCLC carrying exon 19 deletion, afatinib has been shown to offer longer progression free survival (PFS) than gefitinib and erlotinib, but with some more adverse events, namely cutaneous and gastrointestinal adverse events[4]. Afatinib is also approved for the first-line treatment of patients with NSCLC whose tumors bear *EGFR* mutations including S768I, L861Q, and G719X[5].

EGFR T790M mutation is one of the acquired resistance mechanism to first and second generation EGFR-TKI in 50% of cases. Osimertinib is a third generation EGFR-TKI that was approved by the US Food and Drug Administration (FDA) to treat these cases. Its use confers an objective response rate (ORR) of 71%, and a median progression free survival (PFS) of 10.4 months, which were both significantly better than those observed with pemetrexed and platinum-based chemotherapy combination[6]. For patients with central nervous system (CNS) metastases, the median PFS was longer with osimertinib than with chemotherapy by 4.3 months. Osimertinib is now also approved by the US FDA for the first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations. In the FLAURA study, osimertinib demonstrated significant improvement in PFS by 8.7 months and duration of response by 8.7 months relative to gefitinib or erlotinib[7].

Osimertinib was also shown to have superior activity against CNS metastases than first generation EGFR-TKI in first line setting as it has higher cerebrospinal fluid concentration. In subset analysis of the FLAURA study that included treatment-naïve patients with EGFR-mutated advanced NSCLC and CNS metastases, the PFS was longer for patients receiving osimertinib compared with those receiving either gefitinib or erlotinib by 5.6 months. The intracranial response rate was also better for the osimertinib arm, with 91% in the osmertinib arm compared with 68% in the gefitinib or erlotinib arm[8].

ALK-positive NSCLC

There are currently at least three anaplastic lymphoma kinase (*ALK*) inhibitors available in Hong Kong. Crizotinib is used for *ALK*-positive NSCLC which has markedly improved outcomes in patients with *ALK*-positive advanced NSCLC compared to chemotherapy. Upon development of resistance to crizotinib, newer ALK-TKI such as alectinib and ceritinib can be used in the second line setting.

For alectinib, there is evidence suggesting that it may be a better choice than crizotinib in the first-line setting, with better systemic and intra-cranial disease control and a more favorable side effect profile compared with crizotinib. In the J-ALEX trial, alectinib offered significantly longer median PFS than crizotinib with lesser adverse events[9]. Similar findings were also reported in the ALEX and ALESIA trial[10]. Alectinib is particularly effective for patients with brain metastases. Alectinib is also approved by the US FDA for treatment of advanced *ALK*-positive NSCLC that has progressed while on crizotinib.

Ceritinib is a second-generation ALK-TKI that is 20 times more potent than crizotinib. Study has shown that ceritinib 450 mg daily with food to be equivalent to fasting dose of 750 mg daily in terms of efficacy but with less gastrointestinal toxicity[11]. Ceritinib is also active in brain metastasis, with an overall response rate of 54% but its adverse event profile remains a hurdle to successful and tolerable treatment.

Brigatinib and lorlatinib are also being studied on *ALK*-positive NSCLC. They may be available as further treatment options for *ALK*-positive NSCLC patients in near future.

ROS1-rearranged NSCLC

ROS1 translocation or rearrangement occurs in 1 to 2% of NSCLC. It is more commonly seen in younger patients who are never-smokers with adenocarcinoma histology. Due to the homology between the *ALK* and *ROS1* tyrosine kinase domains, *ROS1* rearranged NSCLC is as highly sensitive to crizotinib as for *ALK*-positive NSCLC. US FDA has approved crizotinib as first line treatment for *ROS1* rearranged NSCLC, which has an ORR of 72%, median duration of response of 17.6 months, and median PFS of 19.2 months[12]. Upon disease progression with crizotinib, ceritinib and cabozantinib have been proposed to be possible treatment options, though more data is needed to support their efficacy in *ROS1* rearranged NSCLC. The exception for *ALK* inhibitor in *ROS1* mutated NSCLC is alectinib, which has no *ROS1* inhibitory activity.

BRAF Mutated NSCLC

BRAF is a downstream signaling mediator of *KRAS* that activates the mitogen-activated protein kinase (MAPK) pathway, mediating tumor growth signaling. *BRAF* mutations occur in 1 to 3% of NSCLC. It is more commonly seen in smokers. Combination of dabrafenib plus trametinib has been developed to treat *BRAF* mutated NSCLC and it is approved by US FDA as second line treatment after disease progressed while on chemotherapy. Studies have shown that combination of dabrafenib plus trametinib was associated with an ORR of 63%, disease control rate of 79% and median PFS of 9.7 months in phase II study[13]. The most common side effects include cutaneous toxicities such as dry skin, pruritus, hyperkeratosis, hand-foot syndrome; as well as diarrhea and fever.

Immunotherapy

The development of check-point inhibiting therapy, also known as a type of immunotherapy, brought new hope to patients with squamous cell carcinoma and adenocarcinoma without driver mutation. Immunotherapy for lung cancer can be broadly classified into two groups, anti-programmed cell death 1 (anti-PD1) which includes pembrolizumab and nivolumab,

and anti-programmed death receptor-ligand 1 (anti-PDL1) which consists of atezolizumab. Pembrolizumab is approved by the US FDA for treatment of patients of advanced *EGFR*/*ALK* wildtype NSCLC whose tumors have more than 50% PD-L1 expression. In the KEYNOTE-024 trial, compared with platinum-doublet chemotherapy, pembrolizumab monotherapy provided 4.3 months benefits in median PFS, 6.4 months benefits in median durations of response and 17% improvement in ORR. Pembrolizumab can also be given with platinum-based chemotherapy[14]. US FDA approved the front-line treatment of metastatic non-squamous NSCLC in combination with pemetrexed and carboplatin, irrespective of PD-L1 expression. In the KEYNOTE-189 trial which included advanced, PD-L1-unselected, non-squamous NSCLC patients, the addition of pembrolizumab to chemotherapy improved 12-month overall survival (OS) rates relative to chemotherapy alone by 20% and the improvement was observed in all PD-L1 categories, with the greatest differences in PD-L1-expressing tumors[15].

The addition of bevacizumab to platinum-based doublet chemotherapy and atezolizumab has been studied as well. In the IMpower 150 trial that included patients with PD-L1-unselected advanced non-squamous NSCLC to first-line treatment with chemotherapy consisting of paclitaxel and carboplatin, combined with either atezolizumab, atezolizumab plus bevacizumab, or bevacizumab. The group receiving chemotherapy with atezolizumab plus bevacizumab has better PFS with a 1.5 month difference and OS with a 4.5 month difference compared to the group with chemotherapy with bevacizumab[16]. However, atezolizumab is not yet approved by the US FDA in the first-line setting, although the IMpower 131 trial suggested that atezolizumab plus platinum-doublet chemotherapy provided a PFS benefit of 0.7 months for advanced squamous cell carcinoma of lung in the first line setting compared with carboplatin plus albumin-bound paclitaxel, especially for those with PD-L1 expression more than 50%, but the improvement was not observed in PD-L1-negative tumors.

Nivolumab is approved by US FDA as second line treatment after disease progression with chemotherapy but has not received approval as first line setting yet. There is not enough evidence to support Nivolumab to be used in the first line setting. According to the CheckMate 026 trial, nivolumab did not provide benefits in terms of PFS nor OS when compared with platinum-based chemotherapy[17]. Nivolumab has been evaluated to be used with chemotherapy and anti-cytotoxic T-lymphocyte-associated protein 4 antibody (CTLA-4) named ipilimumab. According to the CheckMate 227 study, in patients with advanced untreated NSCLC high tumor mutational burden, nivolumab plus ipilimumab has better PFS when compared with platinum-based chemotherapy by 1.8 months and ORR is also better by 18%. In the same study, preliminary results suggested that nivolumab with chemotherapy offered longer PFS of 0.9 months when compared with chemotherapy alone in patients with high tumor mutational burden[18].

SUMMARY

In the past decade, the development of lung cancer diagnostics and therapeutics has led to major breakthroughs in the management strategy. Tailor-making the best treatment option for the patient not only relies on the histology, but also the mutation status, metastatic sites as well as patient's performance status. With further development of diagnostic tools and therapeutic agents, we are looking forward to these clinic-pathological as well as molecular profile of lung cancer would transform into better patient tolerance of treatment and survival.

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Precision Medicine in Lung Cancer" by Dr Dr Wang-chun KWOK and Dr David Chi-leung LAM and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 April 2019 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **Molecular test for Epidermal Growth Factor Receptor (EGFR) mutations and Anaplastic Lymphoma Kinase (ALK) expression/rearrangement should be done for all tumors containing an element of adenocarcinoma, regardless of patients' clinical or demographic characteristics.**
2. **The technique of detecting mutations in cell-free circulating tumor DNA in blood (liquid biopsy) is very sensitive and specific and it can replace tissue biopsy for detecting EGFR mutations in non-small cell lung cancer (NSCLC).**
3. **EGFR tyrosine kinase inhibitors (TKI) can be used as 1st line therapy for patients with adenocarcinoma of lung origin irrespective of their EGFR status.**
4. **EGFR T790M mutation is the commonest mechanism of acquired resistance to first and second generation EGFR-TKI and can be effectively managed with Osimertinib.**
5. **Osimertinib is more effective against NSCLC CNS metastases than other EGFR-tyrosine kinase inhibitors.**
6. **Crizotinib is more effective than other ALK-inhibitors in treating brain metastasis from ALK-positive NSCLC.**
7. **NSCLC with ROS1 gene rearrangement can be treated similarly with crizotinib as for ALK-positive NSCLC due to the significant homology between ALK and ROS1 tyrosine kinase domains.**
8. **Checkpoint immunotherapy for NSCLC consists of highly selective humanized monoclonal antibodies directed against programmed cell death-1 or programmed cell death ligand-1 (PD-L1).**
9. **Up to the time of this publication, Pembrolizumab is FDA-approved as 1st line immunotherapy for NSCLC having more than 50% PD-L1 expression.**
10. **Up to the time of this publication, Nivolumab is also approved by FDA as 1st line immunotherapy for NSCLC with documented tumor mutation burden.**

ANSWER SHEET FOR APRIL 2019

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2019 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Precision Medicine in Lung Cancer

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1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐

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Answers to March 2019 Issue

Challenges and Advances in the Prevention and Management of Chronic Kidney Disease

1. T 2. T 3. F 4. T 5. F 6. F 7. F 8. T 9. F 10. T

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FASENRA™ improved FEV_1 after 4 weeks of treatment vs placebo in both SIROCCO and CALIMA Phase III clinical trials*#[2,3]

FASENRA™ is the only biologic that provides near-complete depletion of blood eosinophils in **24 hours**.[1,4,5]

Abbreviated Prescribing Information

Presentation: Benralizumab 30 mg solution for injection in pre-filled syringe. **Indications:** Add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS/LABA. **Dosage:** Subcutaneous injection, 30 mg every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions:** Should not be used to treat acute asthma exacerbations; Seek medical advice if asthma remains uncontrolled or worsens after initiation of treatment; Abrupt discontinuation of corticosteroids after initiation of Benralizumab is not recommended. Reduction in corticosteroid doses should be gradual and performed under the supervision of a physician; Patients with pre-existing helminth infections should be treated before initiating therapy of Benralizumab. **Interactions:** No formal drug interaction studies have been conducted. Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of Benralizumab. **Undesirable Effects:** Headache, pharyngitis, hypersensitivity reactions, pyrexia and injection site reaction. Full local prescribing information is available upon request. API.HK.FAS0518

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* Prebronchodilator FEV_1. The analysis of this endpoint was not multiplicity protected.
# Data for patients with baseline blood eosinophils ≥300 cells per μL in the full analysis set are shown.
FEV_1 = forced expiratory volume in one second.

Please contact (852) 2420 7388 or HKPatientSafety@astrazeneca.com for adverse drug reaction (ADR) reporting to AZHK.
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HK-2263 27/2/2019

ILLUMINATE EOSINOPHILS

REVEAL A TRUE CAUSE OF SEVERE ASTHMA

Elevated eosinophils are seen in the airways of approximately 50% of patients with severe asthma, and are a **direct cause of inflammation**, which can lead to progressive damage in the airways.[1-3]

When patients with severe asthma experience exacerbations requiring systemic corticosteroids, eosinophils may be a driver behind their disease.[3-6] **Testing patients for eosinophilic asthma can help inform clinical decision making.**[3,6,7]

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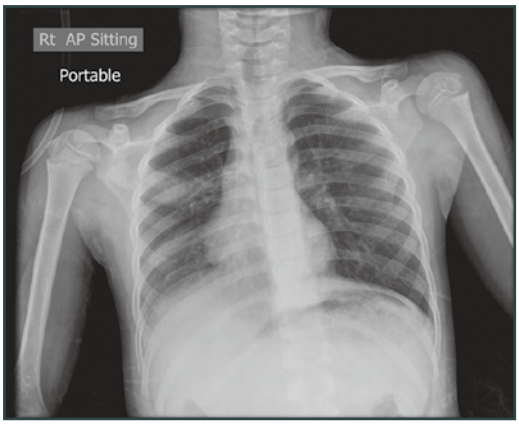
HK-1798 30/08/2018

Radiology Quiz

Dr Michelle CHEUNG

Department of Radiology, Queen Mary Hospital



Please look at the X-ray of the chest of a 7 year old boy presenting with protracted cough and stridor.

1. What are your findings?
2. What is your diagnosis?
3. What are your differentials?
4. What further investigation would you suggest?
5. What is the management and prognosis?

(See P.36 for answers)

Recent Advances in Interventional Pulmonology

Dr Bing LAM

FHKAM (Med), FRCP (Glas.), FRCP (Edin)

Specialist in Respiratory Medicine

Dr Bing LAM

Interventional pulmonology (IP) deals with bronchoscopic and percutaneous procedures for the diagnosis and treatment of both malignant and nonmalignant diseases of the respiratory system. IP has grown significantly in the past decade not only in the diagnostic fields but also in the therapeutic areas.

WHAT IS NEW IN THE DIAGNOSIS OF PERIPHERAL LUNG NODULES?

Along with the widespread use of computed tomography (CT), the detection rate of small lung nodules has increased significantly. This presents a diagnostic challenge to the pulmonologist as the diagnostic yield of conventional transbronchial biopsy is suboptimal[1] yet CT-guided biopsy carries a much higher complication rate[2]. One of the main reasons for suboptimal diagnostic yield of transbronchial biopsy is the failure to find the airway leading to the lesion.

Virtual Bronchoscopic Navigation (VBN)

Just like drivers using the Global Positioning System to find their way to the destination, VBN utilises CT thorax data of the patient to generate three-dimensional virtual images of the airways. These data can be used for either planning or providing navigation during transbronchial biopsy.

Planning

Different VBN systems involve different requirements for slice thickness. Of note is that the thinner the slices, the better can the peripheral airway be demonstrated. For example, the slice thickness should be no more than 1.25 mm if the LungPoint system is used. Once the target lesion is set in these CT images, cross sectional images, the bronchial tree and the automatically selected bronchial routes to the target lesion will be presented (Fig. 1). VBN has been shown to significantly improve the accuracy of endobronchial path selection in a simulation study[3].

Navigation

During the procedure, bronchoscopic view is captured and fed back to the computer. Once the VBN image matches the real image, a navigation line leading to the path will pop up automatically. At the same time, VBN image information on the route and distance to the target lesion are also displayed. From a meta-analysis, the overall diagnostic yield of VBN was 73.8% and that for lesions < 2cm was 67.4% [4].

VBN is also capable of presenting a virtual fluoroscopic view; this is useful especially for lesions which are not visible under fluoroscopy, i.e. small lesions or ground glass opacities (GGO) (Fig. 2). A recent study showed that the addition of virtual fluoroscopy in transbronchial biopsy of GGO could increase diagnostic yield by another 20% [5].

Furthermore, VBN can be easily performed without using expensive consumables such as in the case of electromagnetic navigation.

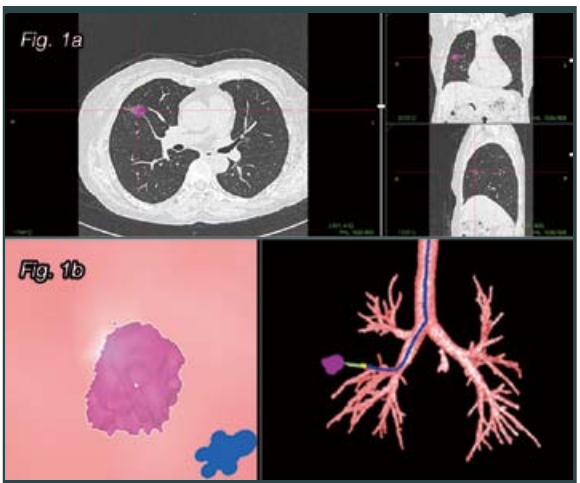


Fig. 1. Right middle lobe lesion with VBN planning.
Fig. 1a. Automatic processing of CT information with the target lesion shown on axial, sagittal and coronal cross-sectional CT images.
Fig. 1b.System-selected bronchial route to the target lesion is presented.

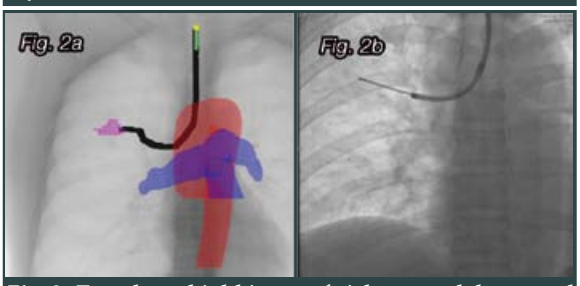


Fig. 2. Transbronchial biopsy of right upper lobe ground glass opacity not visible on fluoroscopy guided by virtual fluoroscopy.
Fig. 2a. Virtual fluoroscopy Fig. 2b. Biopsy under fluoroscopy

NEW indication

Directly switch your patients to Relvar Ellipta for better asthma control outcomes

2x↑ the odds of achieving asthma control*

vs BD ICS/LABA
(70% vs 56%; OR: 1.95, 95% CI: 1.60, 2.38)[1]

24 HRS EFFICACY[2]

vs BD ICS/LABA
12 hours efficacy
with simplified OD dosing[2-10]

20%↓ reduction in exacerbations**

vs FP/SAL
(95% CI: 5, 34%l p=0.014)[11]

Proven superior to BD ICS/LABAs in achieving asthma control

RELVAR ELLIPTA
fluticasone furoate and vilanterol inhalation powder
One-inhalation, once-daily[2]

RELVAR ELLIPTA SAFETY INFORMATION

Warnings and precautions

- Should not be used to treat acute asthma symptoms or an acute exacerbation in COPD.
- Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator.
- Should be used with caution in patients with severe cardiovascular disease.
- An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation.

Adverse reaction

The following adverse events have been reported with a frequency of very common (≥1/10) and common (≥1/100 and <1/10): Pneumonia, influenza, candidiasis of mouth and throat, headache, nasopharyngitis, oropharyngeal pain, sinusitis, pharyngitis, abdominal pain, arthralgia, back pain

RELVAR ELLIPTA ABBREVIATED PRESCRIBING INFORMATION

NAME OF THE PRODUCT RELVAR ELLIPTA **QUALITATIVE AND QUANTITITATIVE COMPOSITION** Pre-dispensed dose of 100mcg or 200mcg of fluticasone furoate and 25mcg vilanterol (as trifenatate). Inhalation powder. **INDICATIONS** Asthma **Relvar Ellipta 100/25mcg & 200/25mcg** is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate: • patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists. • patients already adequately controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist. **DOSAGE AND ADMINISTRATION** Asthma **Adults and adolescents aged 12 years and over** One inhalation of Relvar Ellipta 100/25mcg or 200/25mcg once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. A starting dose of Relvar Ellipta 100/25mcg should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting $beta_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 100/25mcg, the dose can be increased to Relvar Ellipta 200/25mcg, which may provide additional improvement in asthma control. The maximum recommended dose is Relvar Ellipta 200/25mcg once daily. **Children aged under 12 years** The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the indication for asthma. **Elderly patients (>65 years) & renal impairment** No dose adjustment. Relvar Ellipta is for inhalation use only. After inhalation, the patient should rinse their mouth with water without swallowing. Patients should be made aware that Relvar Ellipta must be used regularly, even when asymptomatic. Patients should be regularly reassessed by a healthcare professional so that the strength of Relvar Ellipta they are receiving remains optimal and is only changed on medical advice. **CONTRAINDICATIONS** Hypersensitivity to the active substances or to any of the excipients **WARNINGS AND PRECAUTIONS** Deterioration of disease Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician. Patients should not stop therapy with fluticasone furoate/vilanterol in asthma or COPD, without physician supervision since symptoms may recur after discontinuation. Asthma-related adverse events and exacerbations may occur during treatment with fluticasone furoate/vilanterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with Relvar Ellipta. Paradoxical bronchospasm Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Relvar Ellipta should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. Cardiovascular effects Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease, or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium. Systemic corticosteroid effects Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking Relvar Ellipta 200/25mcg was numerically higher compared with those receiving Relvar Ellipta 100/25mcg or placebo. No risk factors were identified. **INTERACTIONS** Interaction with beta-blockers $Beta_2$-adrenergic blockers may weaken or antagonise the effect of $beta_2$-adrenergic agonists. Concurrent use of both non-selective and selective $beta_2$-adrenergic blockers should be avoided unless there are compelling reasons for their use. Interaction with CYP3A4 inhibitors Caution is advised when co-administering with strong CYP 3A4 inhibitors as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. **PREGNANCY AND LACTATION** Pregnancy Administration of fluticasone furoate/vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Breast-feeding A decision must be made whether to discontinue breast-feeding or to discontinue fluticasone furoate/vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **ADVERSE REACTIONS** Pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, headache, extrasystoles, nasopharyngitis, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, fractures, muscle spasms, pyrexia. **OVERDOSE** There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Abbreviated Prescribing Information based on Relvar Ellipta Hong Kong Prescribing Information HK032018GDS09v2/EMA201803.

* in the intention-to-treat (ITT) population prescribed Seretide at baseline and were either initiated with Relvar Ellipta or continued on Seretide; In the overall population, the difference in reduction of severe asthma exacerbations between Relvar Ellipta and usual care was not statistically significant (0.40 vs 0.41; percentage reduction 2% [95% CI: -9, 12]; p=0.6969).

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Electromagnetic Navigation (EMN)

EMN also utilises the patient's CT scan as the roadmap for planning the procedure.

At the start of the procedure, conventional bronchoscopy is performed to register airway landmarks on the software of the system to link the virtual bronchoscopy with standard bronchoscopy. During the procedure, it uses electromagnetic field to guide a steerable probe to the appropriate bronchial pathway leading to the target. Once the target lesion has been reached, sampling could be carried out. From a meta-analysis, the diagnostic yield of EMN was 73.9%[6]. The diagnostic yield is highly dependent on the presence of bronchus sign on CT imaging[7]. The performance of EMN outside the research setting was reported recently based on the results of the AQuIRE (ACCP Quality Improvement Registry, Evaluation, and Education) registry. The diagnostic yield of bronchoscopy with EMN was only 38.5%[8]. Due to the limitation of registry data, additional data from properly conducted clinical trials are needed. A recently published prospective, multicenter, cohort study evaluated EMN performance in more than 1000 subjects. Follow up was completed in 80% at 12 months with the 12-month diagnostic yield of 73%[9].

Endobronchial Ultrasound with a Guide Sheath (EBUS-GS)

EBUS-GS could obtain real-time high-resolution images of the structures surrounding the airways. Solitary lesions are usually hypoechoic and have a well-defined interface border with normal lung tissue. Therefore, EBUS-GS can help in the localisation of the lesions before sampling to increase the diagnostic yield. Once the lesion is confirmed, the GS is fixed in place and EBUS is replaced by sampling instruments through the GS to sample the lesion. Based on systematic reviews, the overall diagnostic sensitivity of EBUS-GS for peripheral lesions is 73%[10]. Factors identified to be associated with a higher diagnostic yield including: CT bronchus sign, lesion of > 2 cm in diameter, solid nodule and probe position within the lesion[11].

Combining VBN and EBUS-GS has been found to increase the diagnostic yield further, especially for those lesions less than 2 cm in diameter[12].

Ultrathin Bronchoscope

The conventional bronchoscope has an outer diameter ~ 5 mm while ultrathin bronchoscope has a 3 mm outer diameter (Fig. 3). Compared to 4 mm bronchoscope, the ultrathin bronchoscope could reach more distal bronchi (median, fifth-generation bronchi Vs fourth generation) and gave higher diagnostic yield (74% Vs 59%)[13].

The combination of VBN and ultrathin bronchoscope is especially useful for lesions invisible on fluoroscopy and lesions in the peripheral third of the lung field[14].

Bronchoscopic Transparenchymal Nodule Access (BTPNA)

Presence of CT bronchus sign is an important predictor of success in transbronchial biopsy. However, some nodules are eccentrically positioned and may not have an airway directly leading to them[15]. It might not be possible to approach these nodules via the bronchial tree. BTPNA is a novel bronchoscopic technique for accessing nodules through a transparenchymal approach i.e. creating a path leading to the lesion for sampling. Before the procedure, CT data are uploaded to a specific VBN system. Once the target is labeled on the CT film, the system would provide two suitable points of entry (POE) with vessel-free and straight line access to the target. During the procedure, the bronchoscope would be guided to the POE by the navigation system. By using a virtual doppler, bronchoscopists can further fine tune the POE. The system would then integrate fluoroscopic data with the CT data to guide a sheath from POE through the lung parenchyma to the target. The first human study was published in 2015 with a reported diagnostic yield of more than 80%[16].

Fig. 3. Ultrathin bronchoscope (upper) and standard bronchoscope (lower)

WHAT IS NEW IN THE DIAGNOSTIC APPROACH TO MEDIASTINAL LYMPH NODES?

Transbronchial needle aspiration (TBNA) of mediastinal lymph nodes for diagnostic purpose and as a tool for staging of lung cancer was first reported more than 30 years ago[17]. Despite its usefulness, TBNA is not widely used as a result of lack of training or technical reasons[18]. The use of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal lymph nodes was first reported in 2004[19]. By using ultrasound first to identify lymph nodes followed by TBNA under real-time ultrasound guidance, EBUS-TBNA has gained popularity. Compared to more invasive procedures, such as mediastinoscopy, EBUS-TBNA is easier to perform with a low complication rate. EBUS-TBNA also provides access to several lymph node stations that are otherwise difficult or impossible to access with conventional mediastinoscopy. Prospective controlled trial of EBUS-TBNA compared with mediastinoscopy for mediastinal lymph node staging of lung cancer showed similar results[20,21]. Guidelines from

different organisations including American College of Chest Physicians (ACCP)[22], European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS)[23] and National Institute for Health and Care Excellence (NICE)[24] all recommended that EBUS should be the initial staging procedure offered to patients with suspected or proven non-small cell lung cancer (NSCLC) with abnormal mediastinal and/or hilar nodes.

WHAT IS NEW IN THE BRONCHOSCOPIC TREATMENT OF AIRWAY DISEASES?

Bronchial Thermoplasty for Severe Asthma

Bronchial thermoplasty (BT) is a bronchoscopic treatment for severe asthma. The treatment of the airway is delivered in three separate bronchoscope sessions. It works by reducing airway smooth muscle mass via delivering radiofrequency energy to the airway walls[25]. This can decrease the severity of asthma symptoms by decreasing the amplitude of bronchial constriction[26]. A randomised sham controlled study demonstrated that BT in subjects with severe asthma improved asthma-specific quality of life with a reduction in severe exacerbations and healthcare use in the post-treatment period[27].

The US Food and Drug Administration approved BT for the treatment of severe persistent asthma in 2010 for patients >18 years whose asthma is not well controlled with high-dose inhaled corticosteroids and long-acting beta-agonists. The European Respiratory Society (ERS) and American Thoracic Society (ATS) joint Task Force recommend that BT to be performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study in order to provide further evidence of effectiveness and safety of BT[28].

Bronchoscopic Lung Volume Reduction for Emphysema

In the Global Initiative for Chronic Obstructive Lung Disease 2019 (GOLD 2019), endobronchial valves, lung coils and vapour ablation are recommended in selected patients with advanced emphysema.

Endobronchial Valves

One-way endobronchial valves (EBV) (Fig. 4) is supposed to be deployed via the bronchoscope at segmental or sub-segmental bronchi of a pulmonary lobe to attain atelectasis. Since the first randomised controlled trial (RCT) published in 2010[29], multiple studies over the years confirmed that the completeness of fissure and lobar exclusion were predictors of favorable treatment outcome measured by six-minute walk, lung function and quality-of-life (QoL)[30-33]. Regarding complications of EBV treatment, there were no significant differences in mortality compared to control groups, but pneumothoraces were more common in the treatment group[34].

Lung Volume Reduction Coils

Deploying coils into the segmental/subsegmental airways of the target lobe using a special catheter delivery system via the bronchoscope can result in lung volume reduction and improve lung function. The proposed working mechanisms of the coils are:

1) Compression of the lung parenchyma results in less hyperinflation[35];
2) Redistribution of airflow towards healthier parts of the lung[36]; and
3) Improving lung compliance and putting the diaphragm in a better condition of function[37].

Up to now, three randomised clinical trials of coil in treating emphysema have been published and have shown significant improvement in lung function and QoL[38-40]. This treatment can be applied to lobes with collateral flow as well. The reported complications of coil treatment include pneumothorax, COPD exacerbations and pneumonia.

Bronchoscopic Thermal Vapour Ablation

Heated water vapour is applied to pre-selected emphysematous segment(s) through a specially designed balloon catheter via the bronchoscope. The duration of treatment is calculated base on tissue to air ratio of the target segment. The bronchoscopic thermal vapour ablation (BTVA) works by inducing inflammatory reaction followed by scar formation, leading to lung volume reduction in the treated segment(s)[41].

This was first described in 2009[42] and the first RCT was published in 2016[43]. Compared to the control group, the treatment resulted in both objective (FEV 1 improved by ~ 15%) and subjective (SGRQ-C was −9·7 points) improvement. Treatment effect is not affected by collateral flow status[44]. COPD exacerbation was the most common serious adverse event (24% Vs 4%) compared to the control group. Currently, BTVA is a treatment option for patients fulfilling the following criteria: heterogeneous, upper-lobe predominant emphysema, lung function criteria of FEV1 20-45%, residual volume >175%, diffusion capacity >20%; and 6-minute walk test >140 metres[45].

Fig. 4 Endobronchial valve

CONCLUSION

With the rapid advancement in technology, interventional pulmonologists should be able to offer diagnostic and treatment services for all major lung problems in the near future.

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TRELEGY ELLIPTA
fluticasone furoate/umeclidinium/vilanterol

TRELEGY ELLIPTA (FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL)

SAFETY INFORMATION

- Trelegy Ellipta should not be used in patients with asthma since it has not been studied in this population
- Not for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy)
- Use with caution in patients with unstable or life threatening cardiovascular disease
- Do not stop therapy without physician supervision since symptoms may recur after discontinuation

PRESCRIBING INFORMATION

NAME OF THE MEDICINAL PRODUCT TRELEGY ELLIPTA **QUALITATIVE AND QUANTITIVATIVE COMPOSITION** Pre-dispensed dose of 100 micrograms of fluticasone furoate, 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate). Inhalation powder. **INDICATIONS** COPD (Chronic Obstructive Pulmonary Disease) **Trelegy Ellipta** 100 / 62.5 / 25 micrograms is indicated as a maintenance treatment in adult patients with moderate to severe COPD who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β_2-agonist. **DOSAGE AND ADMINISTRATION** COPD Adults aged 18 years and over: One inhalation of **Trelegy Ellipta** 100 / 62.5 / 25 micrograms once daily. Paediatric population: There is no relevant use of **Trelegy Ellipta** in the paediatric population in the indication for COPD. Elderly patients (>65 years), patients with renal impairment or hepatic impairment: No dose adjustment. **CONTRAINDICATIONS** Hypersensitivity to the active substances or to any of the excipients **WARNINGS AND PRECAUTIONS** Asthma **Trelegy Ellipta** should not be used in patients with asthma since it has not been studied in this patient population. Deterioration of disease Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of disease control and patients should be reviewed by a physician. Patients should not stop therapy with **Trelegy Ellipta** without physician supervision since symptoms may recur after discontinuation. Not for acute use **Trelegy Ellipta** is not indicated for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation. Paradoxical bronchospasm As with other inhalation therapies, administration of **Trelegy Ellipta** may produce paradoxical bronchospasm that may be life-threatening. Treatment with **Trelegy Ellipta** should be discontinued immediately if paradoxical bronchospasm occurs. The patient should be assessed and alternative therapy instituted if necessary. Cardiovascular effects Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen with muscarinic receptor antagonists and sympathomimetics, including umeclidinium and vilanterol, respectively. **Trelegy Ellipta** should be used with caution in patients with unstable or life-threatening cardiovascular disease. Hepatic impairment Patients with moderate to severe hepatic impairment receiving **Trelegy Ellipta** should be monitored for systemic corticosteroid-related adverse reactions. Systemic corticosteroid effects Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Visual disturbance Patients with visual disturbance such as blurred vision receiving **Trelegy Ellipta** should be monitored for cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids. Co-existing conditions **Trelegy Ellipta** should be used with caution in patients with convulsive disorders, thyrotoxicosis or pulmonary tuberculosis, or in patients with chronic or untreated infections. Anti-cholinergic activity **Trelegy Ellipta** should be used with caution in patients with narrow-angle glaucoma or urinary retention. Pneumonia in patients with COPD An increase in the incidence of pneumonia, including pneumonia requiring hospitalization has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index and severe COPD. Hypokalaemia β_2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. Caution should be exercised when **Trelegy Ellipta** is used with other medicinal products that have the potential to cause hypokalaemia. Hyperglycaemia β_2-adrenergic agonists may produce transient hyperglycaemia in some patients. Patients with a history of diabetes mellitus receiving **Trelegy Ellipta** should be monitored more closely for hyperglycaemia. Excipients This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **INTERACTIONS** Interaction with β-blockers β_2-adrenergic blockers may weaken or antagonise the effect of β_2-adrenergic agonists. Concurrent use of both non-selective and selective β_2-adrenergic blockers should be avoided unless there are compelling reasons for their use. Interaction with CYP3A4 inhibitors Caution is advised when co-administering with strong CYP3A4 inhibitors as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects, in which case patients should be monitored for systemic corticosteroid side effects. Other antimuscarinics and β_2-adrenergic agonists Co-administration of **Trelegy Ellipta** with other long-acting muscarinic antagonists or long-acting β_2-adrenergic agonists has not been studied and is not recommended as it may potentiate the adverse reactions. **PREGNANCY AND LACTATION** Pregnancy Administration of **Trelegy Ellipta** to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Breast-feeding A decision must be made whether to discontinue breast-feeding or to discontinue **Trelegy Ellipta** therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **ADVERSE REACTIONS** Common: Pneumonia, upper respiratory tract infection, pharyngitis, rhinitis, influenza, nasopharyngitis, headache, cough, arthralgia, back pain; Uncommon: Candidiasis of mouth and throat, viral respiratory tract infection, supraventricular tachyarrhythmia, tachycardia, atrial fibrillation, oropharyngeal pain, fractures. **OVERDOSE** An overdose of **Trelegy Ellipta** will likely produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions. There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Abbreviated Prescribing Information based on Trelegy Ellipta Summary of Product Characteristics, Hong Kong (HK052018, GDS03/EMA20180112).

COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OD, once-daily; UMEC, umeclidinium, VI, vilanterol.

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Update on the Management of Obstructive Sleep Apnoea

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INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a common disorder with prevalence rates of at least 4% among the middle-aged male Caucasians and Hong Kong (HK) Chinese populations[1-3]. It is characterised by repetitive episodes of upper airway obstruction causing intermittent hypoxia and arousals, and leading to systemic inflammation[4], insulin resistance[5], dyslipidemia, hypertension and cardiovascular consequences.[6-8] Proactive management of this condition requires effective treatment targeting at the pathophysiology.

PATHOPHYSIOLOGY OF OSA

Obesity is an important risk factor with OSA prevalence being twice in obese subjects compared to normal weight individuals.[9,10] In one study, a 10% weight gain was associated with a 32% increase in the apnoea-hypopnoea index (AHI).[11] There is increasing prevalence of OSA over the last 20 years according to the latest epidemiological studies, and that could be largely attributable to increasing obesity rates.[12] Apart from obesity, craniofacial factors are well recognised in the pathogenesis of OSA and are likely to play an important role in influencing the response to weight loss. The prevalence of OSA syndrome is as common among the middle-aged HK Chinese population as among Caucasians, despite our Chinese patients having much lower BMI.[3,13] For the same degree of OSA severity, Caucasians are more overweight whereas Chinese exhibit more craniofacial bony restriction.[14,15] Cephalometric measurements based on lateral radiograph of the upper airway have shown that a shorter distance between maxillary projection from the cranial base, a smaller posterior airway space, less mandibular protrusion, a narrower space between the hard palate and cranial base, and a more caudally placed hyoid bone predispose to a higher AHI.[16] There is evidence to show that a shorter mandibular length as measured by lateral cephalometry is associated with a greater fall in AHI after weight loss.[17] Other common risk factors for OSA include male gender and family history. As OSA is known to be a heterogeneous disease with different individual risk factors, clinical presentation and cardiovascular consequences, personalised management towards this condition is particularly important in OSA.

MANAGEMENT OF OSA

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is the first-line treatment for OSA as it is effective in improving airway patency and AHI, resulting in reduced daytime sleepiness.[18] Previous studies showed that effective CPAP improves the neurobehavioural, cardiovascular consequences[19,20] and general measures of quality of life. However, wide variance (25% to 75%) in adherence to this 'gold standard' therapy may be problematic to the effectiveness of the treatment.[21,22] Moreover, previous randomised studies did not show any improvement in visceral adiposity, insulin resistance and metabolic dysfunction after CPAP alone.[23,24] CPAP can be viewed as a 'one size fits all' solution to OSA but the problems of inadequate compliance, including increasing nasal resistance, claustrophobia, other psychological factors and mask intolerance limit the effectiveness of this therapy in the real world.

Weight Reduction

Weight reduction has always been advocated in patients with OSA who are overweight, and this will also likely improve the cardiometabolic abnormalities that often accompany OSA, including insulin resistance and type 2 diabetes mellitus, dyslipidaemia, and hypertension.[25-27] However, despite substantial improvement of OSA symptoms in studies of major weight loss following bariatric surgery, the chance of cure (AHI <5 events/hr) remains low.[28,29] Previous randomised controlled trial of dietician-led lifestyle modification program (LMP) in 104 patients (baseline body mass index (BMI) 30.4± 4.0kg/m2 and AHI 43.2±20 events/hr) proved significant weight loss (BMI change -5.6% vs -1.3%) and lower AHI (-17.8% vs 1.3%) after the first 4 months of intensive counselling and the response was sustained after 8 months.[30] However, a wide variety of response to the therapy was observed, with 21.3% of patients with severe disease that converted to mild to moderate and only 6.6% of those with severe disease who became mild in severity.

Oral Appliances

The concept in oral appliances for OSA patients is enlargement of the upper airway with the mandibular and tongue advancement, and thus reducing upper airway collapsibility. The primary oral appliance (OA) used in OSA treatment is the mandibular advancement device (MAD) which is attached to the upper and lower

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Jointly organised by

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Objectives:

The program is offered for health care professionals with an intention of personal growth and / or professional development by direct personal experience of mindfulness practices. Through experiential learning of various mindfulness meditation practices, participants are invited to explore what mindfulness is and how it may transform our way to relate to stresses and challenges in life and at work.

Completion of this course fulfills the pre-requisite requirement of most local or overseas professional trainings for teaching courses for teaching mindfulness-based interventions (e.g. MBSR or MBCT)

Instructor:

Dr. Chloe Chin, Clinical Psychologist

Dr Chin has completed the teacher trainings for teaching Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT) and Mindful Self-Compassion (MSC). Started teaching mindfulness since 2010, Dr Chin has the experiences of conducting large-scale mindfulness workshops and teaching over 15 courses of 8-week MBSR and MBCT for a variety of clinical and non-clinical participants. She also has experiences of running training workshops and courses in mindfulness for health care professionals.

Date	Time / Duration	Venue	Theme / Content
25 May	10:00am-1:00pm	*(1)	Orientation and Experiential Introduction to Mindful Practices
1 Jun	10:00am-12:30pm	*(1)	Perception and Stress Reactivity
8 Jun	10:00am-12:30pm	*(1)	Living in the Present
15 Jun	10:00am-12:30pm	*(1)	Recognizing Stress Reactive Patterns
22 Jun	10:00am-12:30pm	**(2)	Responding with Mindfulness
29 Jun	10:00am-12:30pm	*(1)	Mindfulness in Communication
6 Jul <1-day class>	10:00am-1:00pm & 2:00pm-6:00pm	*(1)	One-day Retreat for Intensive Mindfulness Practices
13 Jul	10:00am-12:30pm	*(1)	Mindfulness in Daily Life
20 Jul	10:00am-1:00pm	*(1)	Integration and Extending New Learning

No. of session / Duration : 8 weekly sessions and 1 whole-day session, total 28 hours
Date / Time : 25 May & 1, 8, 15, 22, 29 Jun &13, 20 Jul, 2019 (10:00 am-1:00 pm) &
6 Jul, 2019 (10:00am-1:00pm & 2:00pm-6:00pm) Every Saturday
Venue : JAO TSUNG-I ACADEMY鏡宗頤文化館, 800 Castle Peak Road, Lai Chi Kok (near Mei Foo MTR station)
*(1) Block J (修學精舍) & **(2) Block I (演藝廳)
Language Media : Cantonese
Course materials : Guided meditation tapes (in mp3 format) and session notes will be provided
Course Fee : HK$3,500 (Free gift : yoga mat)
Certificate : Certificate of Completion will be awarded to participants with a minimum attendance of 80%
(i.e. 8 out of 10 sessions, whole-day class counted as 2 sessions)
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
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dental arches in a configuration to protrude the lower jaw relative to the upper jaw. Contraindications of using MADs include patients with inadequate number of sound teeth, severe periodontitis, and/or history of temporomandibular joint disease. Although there is significant improvement in AHI with the use of MADs, the use in more severely affected patients is limited. Female OSA patients of younger age, smaller neck circumference, lower body mass index, lower AHI, and supine-dependent are predictors of good response with MADs. However, there are no accurate thresholds for any of these factors to exclude patients from therapy.[31,32]

Upper Airway Surgery

Surgical approach to prevent pharyngeal collapse can be performed by i) reducing soft tissues (e.g. uvulopalatopharyngoplasty, tongue reduction, adeno-tonsillectomy), ii) increasing the size of the bony enclosure (e.g. maxillomandibular surgery), iii) repositioning of the hyoid bone (hyoid repositioning), or increasing nasal patency (e.g. turbinate reduction surgery). There is no evidence regarding the role of surgery in patients with OSA although surgical treatment appears to be most effective in patients with severe, surgically correctable, obstructive lesion of the upper airway, e.g. tonsillar hypertrophy, adenoid hypertrophy, or craniofacial abnormalities.[33]

Treatment of OSA by Phenotypes

Apart from the impaired upper airway anatomy in the pathogenesis of OSA, recent research in OSA phenotyping has identified non-anatomical causes and novel targets for therapy. There are different pathways to OSA with both structural and physiological risk factors that differ in relative importance between individuals. Approximately 70% of patients with OSA have impairment in one or more non-anatomical contributors, namely, impaired upper airway muscle responsiveness, low arousal threshold and exaggerated loop gain response. Although there are new advances in the treatment targeting at different pathways, e.g. hypoglossal nerve stimulation to improve muscle responsiveness, and pharmacological therapies to increase arousal threshold and reduce loop gain response, further studies are needed to confirm the effectiveness. Moreover, a major obstacle to implementation of phenotyping concepts into clinical care is that the current gold standard measurement techniques are too complex and not feasible beyond a research setting.[34] More advances are needed so that a simplified phenotyping tool can be developed for tailored therapy.

In conclusion, OSA is a heterogeneous disorder. There has been substantial progress towards personalised management for OSA regarding the different phenotypes and the identification of new therapeutic agents. Nevertheless, multidisciplinary models of care are needed in enhancing patients' acceptance and compliance with the therapies regardless of which treatment is implemented.

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Respimat® - a Unique Soft Mist™ Inhaler

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Inhale 2 puffs once daily

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Superior improvement in lung function over SPIRIVA®[5-7] & LABA/ICS[8#]

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Superior COPD symptom reduction over SPIRIVA®[7,9-10]

LABA/ICS refers to salmeterol/fluticasone 50/500 µg & 50/250 µg

Abridged Prescribing Information

SPIOLTO® RESPIMAT® (tiotropium & olodaterol)
Indication: Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **Dosage and Administration:** Inhalation of the spray of 2 puffs once daily with Respimat® inhaler (1 puff contains 2.5 mcg tiotropium and 2.5 mcg olodaterol). **Contraindications:** Hypersensitivity to the active substances, atropine or its derivatives, e.g. ipratropium or oxitropium, or any of the excipients. **Warnings and Precautions:** Should not be used in asthma. Not for the treatment of acute episodes of bronchospasm, i.e. as rescue therapy. Inhaled medicines may result in paradoxical bronchospasm. Caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction. Should be cautioned to avoid getting the spray into their eyes. Dry mouth, which has been observed with anti-cholinergic treatment, may in the long term be associated with dental caries. In patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 ml/min), use only if the expected benefit outweighs the potential risk. Caution in patients with a history of myocardial infarction during the previous year, unstable or life-threatening cardiac arrhythmia, hospitalized for heart failure during the previous year or with a diagnosis of paroxysmal tachycardia (> 100 beats per minute). Beta2-adrenergic agonists may produce a clinically significant cardiovascular effect as measured by increases in pulse rate, blood pressure and/or symptoms. Caution in patients with cardiovascular disorders, especially ischaemic heart disease, severe cardiac decompensation, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy, hypertension, and aneurysm, in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval (e.g. QT > 0.44 s), and in patients who are unusually responsive to sympathomimetic amines. Beta2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. Inhalation of high doses of beta2-adrenergic agonists may produce increases in plasma glucose. Caution needs to be taken in case of a planned operation with halogenated hydrocarbon anaesthetics. Should not be used in conjunction with any other medications containing long-acting beta2-adrenergic agonists. As with all medications, immediate hypersensitivity reactions may occur after administration. Should not be used more frequently than once daily. **Undesirable effects:** Common (≥ 1/100 to < 1/10): Dry mouth. Uncommon (≥ 1/1,000 to <1/100): Dizziness, insomnia, headache, atrial fibrillation, palpitations, tachycardia, hypertension, cough, constipation.

For detailed information, please refer to full prescribing information.

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SPO-10-2018-03

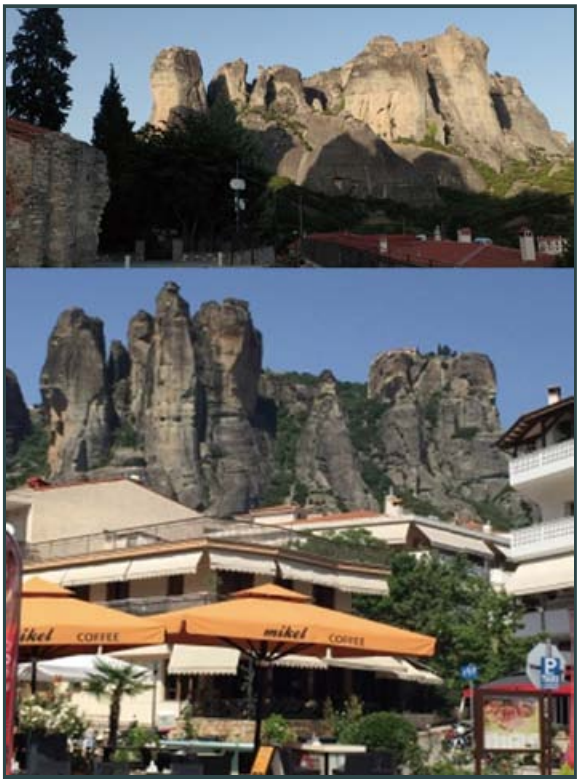
Amazing and Miraculous Meteora

Dr Chun-kong NG

MBBS, MRCP, FHKCP, FHKAM, MPH, FRCP (Edin, Lond)

Consultant Respiratory Physician,
Department of Medicine, Queen Elizabeth Hospital

Dr Chun-kong NG



The beautiful and historical small town of Kalambaka. Hotels and houses are built next to these gigantic rocks.

Greece is a beautiful and magnificent country; glistening blue Aegean Sea, windmill and white houses in Santorini and Mykonos, and the Acropolis of Athens are famous tourist attractions. In addition, the Orthodox Monasteries of Meteora in Northern Greece are equally stunning and breathtaking. Meteoros means "hanging in air" in ancient Greek and it is also nicknamed "天空之城" by visiting tourists. Monks began to settle in this area around the 11th Century. It was not until the 14th Century when the G reek monks started to build monasteries on the top of the gigantic rocks to escape from the Turkish attacks and persecutions. In the past, accesses to these monasteries were extremely difficult if not impossible: by ladders or baskets tied together with ropes hanging alongside the cliff. At the highest peak, 24 monasteries were built and thousands of monks lived here. Today, six monasteries are still functioning and inhabited by monks or nuns. Meteora was listed by the UNESCO as World Heritage in 1988 and is visited by tens of thousands of tourists every year.

There is no direct flight from Athens to Meteora. KETL buses run every day from Liossion Street in Athens to Trikala. After arrival at Trikala, one has to change to local buses that run to Kalambaka, the small village situated at the foot of Meteora rocks. Depending on traffic conditions, the trip may take 5-6 hours.

Megaro Meteoron (Monastery of Great Meteoron) is the largest monastery built on Platys Lithos (the broad rock) by Saint Athanasios the Meteorite in mid-14th Century. Located in the central courtyard, The Katholikon (main cathedral) is embellished with beautiful 16th century frescoes that depict the persecution of Christians by the Romans. Inside the Monastery, you can visit the Museum, the Sacristy, the Kitchen and the Dining Hall. From the monastery lookout, you will see the magnificent and picturesque view of Kastraki town and Varlaam Monastery.

The Monastery of Varlaam is the second largest monastery in Meteora and was founded in the mid-14th Century by Hosios Varlaam. This is the only monastery where you can visit the tower of the preserved net used by the monks to ascend and descend from the rock in the past. Other places to visit are the monastery Catholicon, the museum, bibliographic workshop and workshop of gold-embroidery of the Monastery.

The Monastery of Rousanou was founded in 1545 by Joasaph and Maximos. It was converted to a convent in 1988. Inside the main church, you can find outstanding wall paintings and wood iconostases. To access the church, you have to cross a bridge built between the 2 peaks.

Agia Triada (Monastery of the Holy Trinity) is built on top of the rocky cliffs. One has to walk up 140 steps cut into the rock to get to the monastery. It was founded by the monk Dometius in the 15th Century, with the main Cathedral constructed and painted by the brother priests Antonios and Nicolaos. This monastery has been used to film the James Bond movie "For Your Eyes Only".

Agios Stefanos (Monastery of St. Stephen) is the most easily accessible monastery that requires no climbing. It was founded by St. Antoninus Cantacuzene in the 15th Century and was turned to a convent in 1960. There is a spectacular view of the valley of Thessaly, the river Pinios and the Pindos mountain range.

Visiting all the monasteries in half a day can be very challenging as the monasteries are dispersed far apart. Public buses run between these monasteries but the schedule is very infrequent and there are lots of tourists. The best solution is to hire a taxi for half a day. You will learn the history and all the related scenic information from the local taxi drivers.

Medical Diary of April

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	* HKMA-HKS&H CME Programme 2018-2019 * MPS Workshop - Building Resilience and Avoiding Burnout * HKMA Council Meeting 2	* Course on Community Nephrology (Facebook CME Live) 3	* FMSHK Certificate Course in Cardiology 2019 4	5	6
* Federation Sports Day 2019 – Day 1 7	8	* HKMA Yau Tsim Mong Community Network - Diagnosis and Management of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescent * MPS Workshop - Building Resilience and Avoiding Burnout * FMSHK Officers' Meeting 9	* The Hong Kong Neurosurgical Society Monthly Academic Meeting –Proton therapy – is it a better alternative? * HKMA Shatin Doctors Network - Update in the Management of Idiopathic Pulmonary Fibrosis * HKMA Central, Western & Southern Community Network: Management of Fungal Infection 10	* HKMA New Territories West Community Network: Diabetes Management in Elderly Patients * FMSHK Certificate Course in Cardiology 2019 11	12	* MPS Workshop - Mastering Difficult Interactions with Patients 13
* Federation Sports Day 2019 – Day 2 14	15	* HKMA Kowloon West Community Network: Boosting Infants' Immunity: Latest Approach to Tackle the Resurgence of Pertussis and Rotavirus Infection 16	* Course on Mental Health (Facebook CME Live) 17	* HKFMS Foundation Meeting * FMSHK Executive Committee Meeting 18	19	20
21	22	23	* Course on Mental Health (Facebook CME Live) 24	* HKMA Hong Kong East Community Network - Transforming Diabetes Care: Reducing CV Mortality in Patients with Type 2 Diabetes 25	26	* Refresher Course for Health Care Providers 2018/2019 - Children and Adolescent Mental Health Challenges in Primary Care 27
28	29	30				

Date / Time	Function	Enquiry / Remarks
2 TUE 1:00 PM	**HKMA-HKS&H CME Programme 2018-2019** Organiser: Hong Kong Medical Association; Hong Kong Sanatorium & Hospital; Speaker: Dr. CHAN Wai Ming, Alson; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Department Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop - Building Resilience and Avoiding Burnout** Organiser: Hong Kong Medical Association; Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: The Cityview Hong Kong, 23 Waterloo Road, Kowloon	HKMA CME Department Tel: 2527 8285 3 CME Point
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Christine WONG Tel: 2527 8285
3 WED 2:00 PM	**Course on Community Nephrology (Facebook CME Live)** Organiser: The Hong Kong Medical Association; Chairman: Dr. HO Chung Ping, MH, JP; Speaker: Dr. CHAN Siu Kim	Mr. Jeff CHENG Tel: 2527 8285 1 CME Point
4 THU 7:00 PM	**FMSHK Certificate Course in Cardiology 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
7 SUN	**Federation Sports Day 2019 – Day 1** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Ying Wah College	Ms Sara CHEUNG Tel: 2527 8898 sara.cheung@fmshk.org
9 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network - Diagnosis and Management of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescent** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Ching Pong; Speaker: Dr. TANG Man Ho; Venue: Crystal Ballroom, 2/F, The Cityview Hong Kong, 23 Waterloo Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
6:30 PM	**MPS Workshop - Building Resilience and Avoiding Burnout** Organiser: Hong Kong Medical Association; Medical Protection Society; Speaker: Dr. FUNG Shu Yan, Anthony; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Department Tel: 2527 8285 3 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
10 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting – Proton therapy – is it a better alternative?** Organizer : Hong Kong Neurosurgical Society; Chairman : Dr YAM Kwong Yu; Speaker(s) : Dr HE Zhexi; Venue : Seminar Room, G/F, Block A, Queen Elizabeth Hospital	1.5 points College of Surgeons of Hong Kong Dr. WONG Sui To Tel: 2595 6456 Fax. No.: 2965 4061
1:00 PM	**HKMA Shatin Doctors Network - Update in the Management of Idiopathic Pulmonary Fibrosis** Organiser: HKMA Shatin Doctors Network; Chairman: Dr. MAK Wing Kin; Speaker: Dr. WONG Wing Ching; Venue: Diamond Room, 2/F, Royal Park Hotel, 8 Pak Hok Ting Street, Shatin	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Central, Western & Southern Community Network: Management of Fungal Infection** Organiser: HKMA Central, Western & Southern Community Network; Chairman: Dr. TSANG Kin Lun; Speaker: Dr. HO Ka Keung; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	Miss Antonia LEE Tel: 2527 8285 1 CME Point
11 THU 1:00 PM	**HKMA New Territories West Community Network: Diabetes Management in Elderly Patients** Organiser: HKMA New Territories West Community Network; Chairman: Dr. TSUI Fung; Speaker: Dr. TSANG Man Wo; Venue: Pak Loh Chiu Chow Restaurant, Shop A316, 3/F, Yoho Mall II, Yuen Long	Miss Antonia LEE Tel: 2527 8285 1 CME Point
7:00 PM	**FMSHK Certificate Course in Cardiology 2019** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Lecture Hall, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wan Chai, Hong Kong	The Secretariat of FMSHK Tel: 2527 8898 Fax: 2865 0345
13 SAT 2:30 PM	**MPS Workshop - Mastering Difficult Interactions with Patients** Organiser: Hong Kong Medical Association; Medical Protection Society; Speaker: Dr. CHENG Ngai Shing, Justin; Venue: HKMA Central Premises, Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road, Central	HKMA CME Department Tel: 2527 8285 3 CME Point
14 SUN	**Federation Sports Day 2019 – Day 2** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Ying Wah College	Ms Sara CHEUNG Tel: 2527 8898 sara.cheung@fmshk.org
16 TUE 1:00 PM	**HKMA Kowloon West Community Network: Boosting Infants' Immunity: Latest Approach to Tackle the Resurgence of Pertussis and Rotavirus Infection** Organiser: HKMA Kowloon West Community Network; Chairman: Dr. LEUNG Kin Nin, Kenneth; Speaker: Dr. TONG Kai Sing; Venue: Fulum Palace, Shop C, G/F, 85 Broadway Street, Mei Foo Sun Chuen	Miss Antonia LEE Tel: 2527 8285 1 CME Point
17 WED 2:00 PM	**Course on Mental Health (Facebook CME Live)** Organiser: The Hong Kong Medical Association; Chairman: Dr. LEE Fook Kay, Aaron; Speaker: Dr. WONG Yee Him	Ms. Tracy GUO Tel: 2527 8285 1 CME Point
18 THU 7:00 PM	**HKFMS Foundation Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898

Date / Time	Function	Enquiry / Remarks
18 THU 8:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
24 WED 2:00 PM	**Course on Mental Health (Facebook CME Live)** Organiser: The Hong Kong Medical Association; Chairman: Dr. LAM Wing Wo; Speaker: Dr. Cindy CHIU	Ms. Tracy GUO Tel: 2527 8285 1 CME Point
25 THU 1:00 PM	**HKMA Hong Kong East Community Network - Transforming Diabetes Care: Reducing CV Mortality in Patients with Type 2 Diabetes** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. KONG Wing Ming, Henry; Speaker: Dr. Myles CHAN; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, HK	Ms. Candice TONG Tel: 2527 8285 1 CME Point
27 SAT 2:15 PM	**Refresher Course for Health Care Providers 2018/2019 - Children and Adolescent Mental Health Challenges in Primary Care** Organiser: Hong Kong Medical Association, HK College of Family Physicians & HA-Our Lady of Maryknoll Hospital; Speaker: Dr. LAM Wing Wo; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin	Ms. Clara TSANG Tel: 2354 2440 2 CME Point

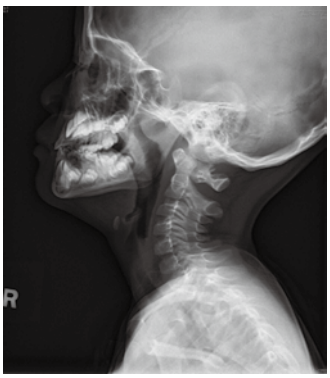
Upcoming Event

10-12 May 2019	**The 20th Regional Osteoporosis Conference (ROC 2019)** Organiser: The Osteoporosis Society of Hong Kong Venue: Main Conference (11 May): Hong Kong Convention and Exhibition Centre IOF & IFCD Course (10 & 12 May): The Harbourview	ROC 2019 Conference Secretariat Tel: 2559 9973 Fax: 2547 9528

Answers to Radiology Quiz

Answers:

1. This is an AP radiograph of the chest. It demonstrates tapering of the upper trachea, consequence of mucosal oedema resulting in tracheal narrowing. It is reminiscent of a church steeple, thus also known as "Steeple sign". A corresponding lateral x-ray would show narrowing of the subglottic trachea and ballooning of the hypopharynx (see below).



2. Croup, also called acute laryngotracheobronchitis. It is commonly due to viral infection of the upper airway by parainfluenza virus or respiratory syncytial virus (RSV).

3. - Tracheal foreign body aspiration
   - Oesophageal foreign body
   - Angioneurotic oedema
   - Epiglottitis (enlargement of epiglottis and aryepiglottic folds; "thumb sign" on lateral neck xray)
   - Congenital subglottic stenosis

   All the above differentials will usually have a slightly different clinical course and history.

4. Radiographs are usually obtained to exclude other causes of a similar presentation. Consequently, once the above described findings are seen on the radiograph, and together with the clinical picture and findings, the diagnosis can often be made clinically and further diagnostic investigations are usually not required.

5. Croup is usually self-limiting and has a good overall long-term prognosis. Treatment is directed toward improving air exchange. Conservative measures, nebulised adrenaline (epinephrine) and corticosteroids are commonly used.

Dr Michelle CHEUNG
Department of Radiology, Queen Mary Hospital

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FDA核准疫苗[1] 適合2歲至49歲人士[2] 成效與一般針劑疫苗相若[3]

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Please contact (852)2420-7388 or HKPatientSafety@astrazeneca.com for adverse drug reactions (ADR) reporting to AZHK

Reference: 1. Centres for Disease Control and Prevention. https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_w. Accessed on 17 December 2018. 2. Quadrivalent intranasal live influenza vaccine HK Prescribing Information. August 2018 Buchan SA et al. JAMA Paediatric 2018; doi:10.1001/jamapediatrics.2018.1514.

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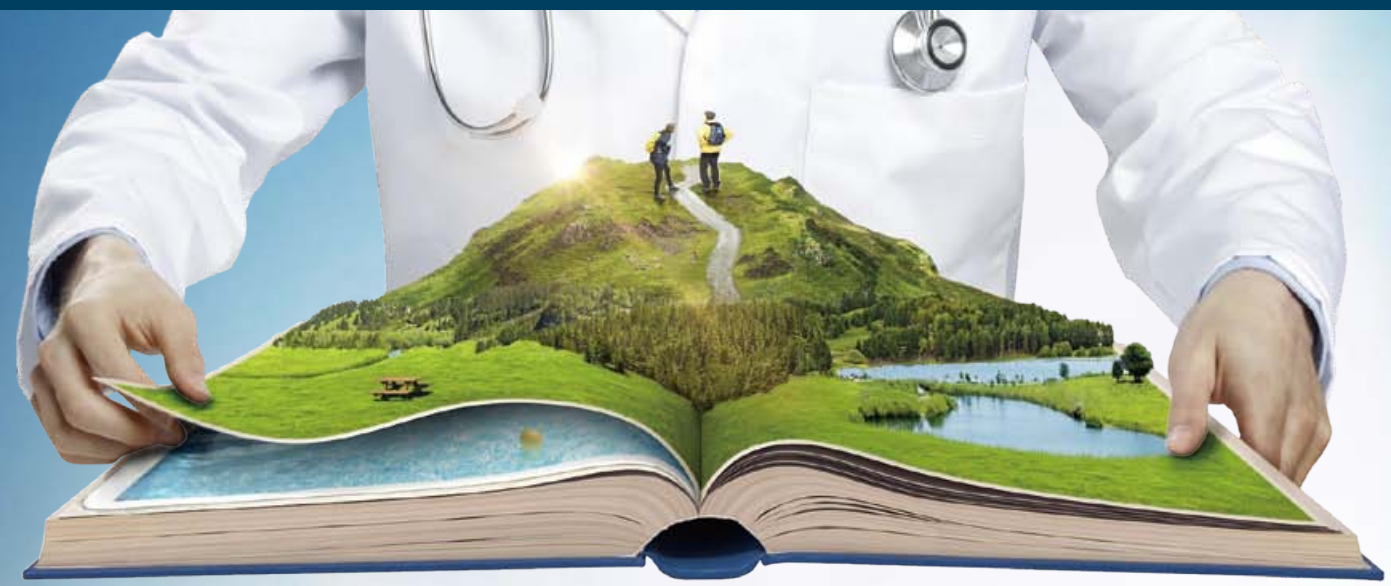

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Vs Tiotropium[2]	Vs Fluticasone / Salmeterol[3]
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ULTIBRO™ BREEZHALER® **Important note:** Before prescribing, consult full prescribing information. **Presentation:** Inhalation powder hard capsules containing indacaterol maleate equivalent to 110 microgram (mcg) indacaterol and glycopyrronium bromide equivalent to 50 microgram glycopyrronium. **Indications:** Ultibro Breezhaler is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD), and for the reduction of exacerbations of COPD in patients with a history of exacerbations. **Dosage: Adults:** recommended dosage is the once-daily inhalation of the content of one 110/50 mcg capsule using the ULTIBRO BREEZHALER inhaler. **Children (<18 years):** should not be used in patients under 18 years of age. **Special patients population:** *Renal impairment:* can be used at recommended dose in patients with mild to moderate renal impairment. Should be used only if expected benefit outweighs the potential risk in patients with severe renal impairment or end-stage renal disease requiring dialysis. *Hepatic impairment:* Can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment. *Geriatrics:* can be used at recommended dose in patients 75 years of age and older. **Method of administration:** ULTIBRO BREEZHALER capsules must be administered by the oral inhalation route and only using the ULTIBRO BREEZHALER inhaler. Capsules must not be swallowed. ULTIBRO BREEZHALER should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day. Capsules must always be stored in the blister to protect from moisture, and only removed immediately before use. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **Contraindications:** ◆Known hypersensitivity to indacaterol, which is one of the components of ULTIBRO BREEZHALER, or to any of the excipients. Ultibro Breezhaler capsules contain lactose. Therefore, patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not take this medicine. **Warnings/Precautions:** ◆**ULTIBRO BREEZHALER** should not be administered concomitantly with other long-acting beta-agonists or long-acting muscarinic-antagonists. ◆**asthma:** should not be used in asthma, long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for treatment of asthma ◆**not for acute use:** should not be used as rescue therapy ◆**hypersensitivity related to indacaterol:** If hypersensitivity reaction occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆**paradoxical bronchospasm:** as with other inhalation therapy, administration may result in paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆anticholinergic effects related to glycopyrronium: use with caution in patients with narrow-angle glaucoma and urinary retention ◆**systemic effects of beta-agonists:** as with other beta$_2$-adrenergic agonists, should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension); in patients with convulsive disorders or thyrotoxicosis; in patients who are unusually responsive to beta$_2$-adrenergic agonists ◆**patients with severe renal impairment:** to be used only if expected benefit outweighs potential risk in patients with severe renal impairment including end-stage renal disease requiring dialysis. ◆**cardiovascular effects of beta-agonists:** like other beta$_2$-adrenergic agonists, may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms. ECG changes ◆**hypokalemia with beta-agonists:** beta$_2$-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias ◆**hyperglycemia with beta agonists:** clinically notable changes in blood glucose (4.9%) at the recommended dose than on placebo (2.7%). ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled. **Pregnancy:** should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus. **Breast-feeding:** should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **Fertility:** No studies on the effect on fertility have been conducted with the indacaterol/ glycopyrronium combination. **Labor and delivery:** Information related to indacaterol - ULTIBRO BREEZHALER may inhibit labor due to a relaxant effect on uterine smooth muscle. **Interactions:** ◆No specific drug-drug interaction studies were conducted with ULTIBRO BREEZHALER. Information on the potential for interactions is based on the potential for each of its two components. ◆should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use ◆should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT-interval. Drugs known to prolong the QT-interval may increase the risk of ventricular arrhythmia. ◆concomitant administration of other sympathomimetic agents may potentiate the undesirable effects ◆concomitant treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalemic effect of beta$_2$-adrenergic agonists. ◆inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses. ◆co-administration with other inhaled anticholinergic-containing drugs has not been studied and is therefore not recommended. ◆no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport. **Adverse reactions:** *Adverse reactions from ULTIBRO BREEZHALER* ◆**Very common (≥10%):** Upper respiratory tract infection ◆**Common (≥1% to <10%):** Nasopharyngitis, urinary tract infection, sinusitis, rhinitis, hypersensitivity, diabetes mellitus and hyperglycemia, dizziness, headache, cough, oropharyngeal pain including throat irritation, dyspepsia, dental caries, bladder obstruction and urinary retention , pyrexia, chest pain ◆**Uncommon (≥0.1% to <1%):** Insomnia, glaucoma, ischemic heart disease, atrial fibrillation, tachycardia, palpitations, epistaxis, paradoxical bronchospasm, dry mouth, gastroenteritis, pruritus/rash, musculoskeletal pain, muscle spasm, pain in extremity, myalgia, peripheral edema, fatigue. ◆**Rare (≥0.01% to <0.1%):** Paraesthesia **Packs:** 30 Inhalation Powder Hard Capsules/Pack **Legal classification:** P1S1S3 Ref: TGA Feb 2018 (0809s)

References: 1. Ultibro Breezhaler Local Prescription Information 2018. **2.** Wedzicha JA, et at. Lancet Respir Med 2013;1:199-209. **3.** Wedzicha JA, et al. N Eng J Med 2016;374:2222-2234. **4.** Anoro Ellipta - Prescription Information **5.** Duaklir Genuair - Prescription Information **6.** Spiolto Respimat -Prescription Information

Full Prescribing Information is available on request

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