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Difficult and Severe Asthma

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Abbreviations: LUTS: lower urinary tract symptoms; **OAB**: overactive bladder

References: 1. Wagg A, *et al*. Efficacy, safety and tolerability of mirabegron in patients aged ≥ 65 yr with overactive bladder and a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). *Eur Urol*. 2020;77(6):711-20. 2. Gooding TL, *et al*. Effect of mirabegron on cognitive function in elderly patients with overactive bladder: MoCA results from a pilot 4 randomised, placebo-controlled study (PILLAR). *BMC Geriatr*. 2020;20(1):143. 3. Chapple CR, *et al*. Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: a retrospective observational study in UK clinical practice. *Eur Urol*. 2017;72(3):389-96.

Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 2.0 **Composition:** Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly: 25 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew and crush. **Contraindications:** Mirabegron is contraindicated in patients with: - Hypersensitivity to the active substance or to any of the excipients. - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment Betmiga has not been studied in patients with renal stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Dose use limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²): based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron to these patients. Patients with bladder outlet obstruction and patients taking antimuscarinic medications for OAB Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in post-marketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 5,683 patients with OAB, of which 5,444 received at least one dose of mirabegron in the phase 2/3 clinical program, and 4,022 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double-blind, placebo controlled studies, 98% of the patients completed treatment with Betmiga and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double-blind, placebo-controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long-term) active-controlled (vs. eccentric antagonist) study, were similar in type and severity to those observed in the three 12-week phase 3 double-blind, placebo controlled studies. List of adverse reactions The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double-blind, placebo-controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Infections and infestations: Common:** Urinary tract infection, Sinusitis, Vaginal infection, Cystitis **Psychiatric disorders: Not known (cannot be estimated from the available data):** Insomnia **Eye disorders: Rare:** Eyelid oedema **Cardiac disorders: Common:** Tachycardia, Palpitation **Vascular disorders: Very rare:** Hypertensive crisis* **Gastrointestinal disorders: Common:** Nausea*, Constipation*, Diarrhoea* **Uncommon:** Dyspepsia, Gastritis **Rare:** Lip oedema **Skin and subcutaneous tissue disorders: Uncommon:** Urticaria, Rash, Rash maculo, Rash papular, Pruritus **Rare:** Leucocytoclastic vasculitis, Purpura, Angioedema* **Musculoskeletal and connective tissue disorders: Uncommon:** Joint swelling **Reproductive system and breast disorders: Uncommon:** Vulvovaginal pruritus **Investigations: Uncommon:** Blood pressure increased, GGT increased, ALT increased, AST increased **Renal and urinary disorders: Rare:** Urinary retention* **Nervous system disorders: Common:** Headache*, Dizziness* *Observed during post-marketing surveillance **Pill prescribing information is available upon request.**

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The Cover Shot

Delicate Arch is located in the Arches National Park north of Moab, state of Utah, the United States of America. This 46-feet tall stone arch is the iconic symbol of the state of Utah and is one of the world's most famous geological features, attracting countless tourists every year. The trip to Delicate Arch from Wolfe Ranch parking is a 4.8-km roundtrip hike that requires climbing up a steep slickrock slope and at least 1.5 -2 hours to complete. The sunset scenery is particularly stunning when the Arch is illuminated fiery red by the receding sun.

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Editorial

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Editor

Dr Chun-kong NG

Asthma is a prevalent airway disease affecting 4.3% of the world population. It was estimated that 17% of asthma patients taking medium- to high-dose inhaled corticosteroids (ICS) had difficult-to-control asthma, which is defined by the Global Initiative for Asthma (GINA) as having uncontrolled asthma despite receiving medium- to high-dose ICS together with controller medications. Incorrect diagnoses, inhaler-related problems and co-morbidities may co-exist and contribute to poor asthma control. It is essential to identify and remove these contributing factors timely in order to achieve optimal asthma control. On the other hand, severe asthma is defined by GINA as uncontrolled asthma despite patients' optimal compliance with maximal treatment and clinical management of all the contributing factors. Although severe asthma is present in 4.3% of patients, it consumes a significant proportion of healthcare resources and leads to significantly higher adverse clinical outcomes, including mortality.

In this issue of the Medical Diary, local asthma experts are invited to share their experiences in the management of difficult and severe asthma. Dr KP CHAN and Dr Fanny KO from Prince of Wales Hospital will introduce the concept of asthma phenotypes and talk about the locally available biomarkers commonly used to phenotype asthma patients. Dr Herbert KWOK and Dr David LAM from Queen Mary Hospital will focus their discussions on using medications (including biologics) to manage the eosinophilic type of asthma. Dr YC YEUNG from Princess Margaret Hospital will talk about the other spectrum of disease, non-eosinophilic asthma, covering both medical and non-drug management. Dr CT LUN from Alice Ho Miu Ling Nethersole Hospital and Dr WK LAM from North District Hospital will discuss pregnancy in asthma patients and choices of appropriate medications for pregnant asthma patients. Last but not least, Dr Cynthia LEE and Dr Grace LAM from Pamela Youde Nethersole Eastern Hospital will discuss ventilatory supports for asthma patients suffering from severe exacerbations and respiratory failure.

Through this contemporaneous review, I hope our Medical Diary readers will acquire more in-depth understanding on this fast-evolving and advancing field, and will apply this knowledge in the management of their asthma patients. Finally, I would like to express my sincere gratitude to all the authors of this issue for their invaluable supports and knowledge sharing.

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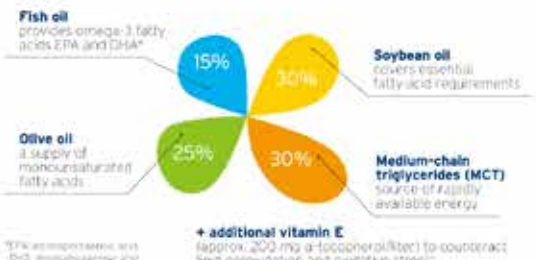

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Severe Asthma: Phenotyping and Its Implication for Treatment

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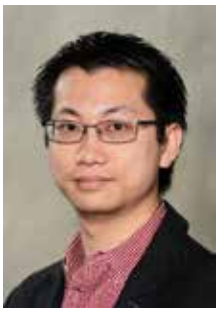

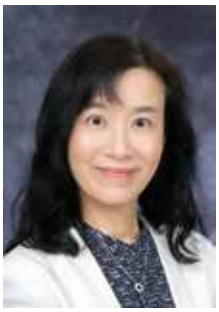

Dr Ka-pang CHAN Dr Fanny WS KO

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 June 2022.

INTRODUCTION

Asthma is the most common non-infectious respiratory disease globally with heterogeneous presentation. There is currently clear evidence of different patterns of airway inflammation in patients with asthma, and complete symptom control is not always achievable in many patients, even with inhaled corticosteroids (ICS).[1] Patients with severe asthma had higher total and asthma-related outpatient visits, inpatient days, emergency room visits and costs per patient-year than those with non-severe asthma.[2,3] The Lancet Asthma Commission gave seven major recommendations in 2018 incorporating the concept of personalised asthma management given the unchanged mortality and stalling outcomes of asthma.[4] Phenotyping would help the management of patients with severe asthma, and this article will provide a brief review of phenotyping and its implication for the treatment of severe asthma.

SEVERE ASTHMA

Severe asthma is defined as asthma that is uncontrolled despite patient adherence with maximal optimised therapy (high-dose ICS plus a second controller) and optimal management of contributory factors, or as asthma that worsens when high-dose treatment is decreased.[5,6] To make a diagnosis of severe asthma, contributory factors including suboptimal drug compliance, inadequate adherence to medical recommendations, poor inhaler techniques for drug delivery, ongoing triggers for asthma (e.g. occupational triggers), comorbidities-related symptoms (e.g. gastro-oesophageal reflux disease, rhinitis) and asthma mimics (e.g. vocal cord dysfunction, chronic obstructive pulmonary disease [COPD], eosinophilic granulomatosis with polyangiitis [EGPA]) should have been adequately addressed and managed.[6] About 5-10% of patients with asthma suffer from severe disease [Chung 2014]. A recent study found that large numbers of asthma patients in the United Kingdom with potential severe asthma (8%) are effectively hidden in primary care pool without referral or specialist review in the previous year.[7] The prevalence of severe asthma can be significantly reduced to 3 to 4% if poor drug adherence and inhaler technique can be optimised[8] , by reinforcing the need to review patient treatment compliance during every clinic visit. In severe uncontrolled asthma, further treatment escalation should be individualised based on asthma phenotyping by respiratory specialists with expertise in asthma management.[6] A detailed account of phenotype-based treatment can be found in other articles in this issue of the Hong Kong Medical Diary.

BIOMARKERS FOR PHENOTYPING

The key principle of phenotyping in asthma is to identify whether the asthma follows a T2-high or T2-low inflammatory pathway. The T2 pathway was previously known as Th2 as it was thought to be related to type 2 T-helper cells. However, the nomenclature was changed after the discovery of type 2 innate lymphoid cells as the potent source of interleukin (IL)-4, 5, and 13 and other type 2 cytokines.[10] The whole process of phenotyping starts with clinical history and examination, whereby one identifies the course of disease development, age of asthma onset, body weight, presence of comorbidities (e.g. nasal polyposis) and atopic diseases (e.g. allergic rhinitis, eczema), prior response to steroids, together with the measurement of T2 biomarkers including sputum inflammatory cells, blood eosinophil count (BEC) and fractional exhaled nitric oxide (FeNO).

Sputum inflammatory cells

Eosinophil and neutrophil levels can both be measured in induced sputum, which directly reflects the inflammatory process in the airway. Sputum eosinophilia (≥ 3%) correlates with airway eosinophilia.[11] Its amplitude was positively associated with post-bronchodilator forced expiratory volume in 1 second (FEV1) in asthmatic patients. In contrast, high variability in sputum eosinophil count rather than its amplitude at baseline or over time was associated with accelerated FEV1 decline and more asthma exacerbations.[12,13] A persistently mixed granulocytic profile (predominantly ≥ 2% sputum eosinophils in combination with ≥ 50% neutrophils is associated with lung function decline and resistance to ICS. Sputum eosinophilia predicts a good response to ICS or a course of oral corticosteroids (OCS)[14], and treatment of patients based on sputum eosinophil counts showed a reduction in exacerbation rates, especially in those with severe asthma.[15] Both European Respiratory Society/American

Thoracic Society (ERS/ATS) and Global Initiative for Asthma (GINA) guidelines support the use of sputum eosinophils for severe asthma management.[5,6] However, sputum induction and examination are expensive and may not be readily available in the primary care setting.[16] When available, the results can complement the diagnostic work-up and phenotyping for severe asthma.[6]

In large cohorts of patients across the whole severity spectrum, pauci-granulocytic and eosinophilic asthma were the two most frequently encountered phenotypes where the proportion of eosinophilic asthma increases with disease severity. In contrast, pauci-granulocytic asthma is the most prevalent inflammatory phenotype in mild asthma, even if sputum analysis suggests that pauci-granulocytic asthma is low-grade eosinophilic airway inflammation.[17]

Blood eosinophil count (BEC)

BEC is one of the most important and readily accessible T2 biomarkers. Minimum BEC to identify T2-high severe asthma ranges from 150 to 300 cells/μL. Many biomarkers were evaluated in the anti-IL-5 drug trials, but none were deemed superior to blood eosinophil count.[18-20] It is a practical alternative to and a promising surrogate biomarker for sputum eosinophil in asthma phenotyping.[17] There is a close relationship between blood and sputum eosinophil counts[18], with high BEC levels predicting airway eosinophilia[19,20], although not the other way round[21,22]. A single measurement of BEC of at least 150 cells/μL was shown to predict subsequent measurements on average of at least 150 cells/μL in 85% of patients[23]. Therapeutic trials targeting the IL-5 (e.g. mepolizumab, reslizumab, benralizumab) and IL-4/13 (dupilumab) pathways had confirmed their therapeutic effects were dependent on the BEC levels starting from 150 to 400 cells/μL[18,24-28], with higher levels predicting better treatment efficacy in certain types of biologics (mepolizumab and benralizumab)[29,30]. One should be cautious about the interpretation of blood eosinophil levels as it may be affected by various factors, including parasitic infections, use of OCS, and other eosinophil-mediated diseases (e.g. eczema, EGPA). That brings up the important reminder of excluding parasitic infections before the initiation of biologics.

Fractional exhaled nitric oxide (FeNO)

FeNO measures allergic airway inflammation mediated through allergen-driven IL-4 and IL-13 effects on airway epithelial cells and is associated with the extent of airway eosinophilic inflammation.[31] FeNO is convenient in the form of a point-of-care test at a moderate cost.[32] The latest ERS guideline considered FeNO part of the work-up in diagnosing asthma if initial spirometry combined with bronchodilator reversibility testing fails to show airway obstruction.[17] A cut-off value of 40 parts per billion (ppb) offers the best compromise between sensitivity and specificity, while a cut-off value of 50 ppb carries a high specificity of over 90% and supports a diagnosis of asthma.[17] FeNO more than 50 ppb in adults suggests the presence of T2-high inflammation, whereas FeNO less than 25 ppb suggests a T2-low process. High FeNO level has been associated with increased risk of exacerbation, poor symptom control, healthcare resource consumption and ICS response.[33,34] In patients with severe asthma refractory to treatment, FeNO more than 19 ppb is indicative of sputum eosinophilia.[35] Currently there is no consensus on the use of FeNO to guide treatment[5,6,36,37], but it is a valuable biomarker when deciding on the use of biologics in severe asthma.[6] The FeNO level is dependent on body height, gender, ethnicity[38,39], atopy, smoking status, airway calibre, treatment with ICS and anti-IL4/IL13-receptor alpha antibody[17].

DIFFERENT ASTHMA PHENOTYPES

Continuous progress in asthma research related to phenotype and endotype has been made in the past decade. Phenotype refers to the set of observable characteristics of an individual resulting from the interaction of its endotype with the environment, which can be clinically identified by demographic, clinical or pathophysiological characteristics.[4,6] The clinical utility of phenotyping is significant as it can guide personalised treatment. Endotype refers to a subtype of a condition defined by a distinct functional or pathobiological mechanism. Although all the possible molecular biomarkers may not be readily accessible in clinical settings, the study of endotypes is essential in understanding gene expression, inflammatory characterisations and long-term development of therapeutic armamentarium.[4,9]

A composite of clinical indicators and multiple T2 biomarkers are commonly included in deciding the asthma phenotype (Box 1).[6,40] Although various phenotypic patterns have been described using different parameters[41], clinically important asthma phenotypes can be broadly divided into eosinophilic (T2-high; further into allergic and non-allergic) and non-eosinophilic (T2-low; mainly neutrophilic) asthma, which practically guides the use of biologic therapies.[6,33] Eosinophilic asthma is driven primarily by T2 cytokines.[10] T2 inflammation usually rapidly improves with ICS. However, patients with T2-high severe asthma may not respond well despite treatment with high dose ICS.[6] Allergic eosinophilic asthma is characterised by early-onset atopic diseases, high IgE levels and the presence of aeroallergen allergy. Non-allergic eosinophilic asthma is often late-onset, with nasal polyposis and salicylate sensitivity, higher blood and airway eosinophil concentrations, and the IgE is frequently not elevated.[10,42] Non-eosinophilic asthma lacks T2-driven inflammation but has a neutrophilic predominance in the airways. Patients who repeatedly demonstrate no elevations in T2 biomarkers would be considered non-eosinophilic asthma.[43] It is recommended that BEC and FeNO can be repeated up to 3 times before assuming that the asthma is non-eosinophilic.[6] Furthermore, specific non-invasive biomarkers (e.g. volatile organic compounds) are not commonly available in clinical practice, and the blood neutrophil levels do not correlate with sputum neutrophil levels.[40] Non-eosinophilic asthma is often associated with smoking, obesity and occupational exposures, with a poor clinical response to escalating corticosteroid therapy.[40,43]

Table1. Defining eosinophilic and non-eosinophilic asthma using T2 biomarkers (Adapted from Global Initiative for Asthma. Diagnosis and management of difficult-to-treat and severe asthma: https://ginasthma.org/severeasthma/, accessed on 14 Apr 2022; Hinks TSC, Levine SJ, Brusselle GG. Treatment options in type-2 low asthma. Eur Respir J. 2021 Jan 21;57(1):2000528) [6,40]

Eosinophilic (T2-high) asthma
• Blood eosinophils ≥ 150 cells/μL, and/or
• FeNO ≥ 20-25 ppb, and/or
• Sputum eosinophils ≥ 2%, and/or
• Asthma is clinically allergen-driven, and/or
• Need for maintenance oral corticosteroids
Non-eosinophilic (T2-low) asthma
• Blood eosinophils < 150 cells/μL, or
• FeNO < 25 ppb, or
• Sputum eosinophils < 2%

Two cross-sectional phenotyping studies using asthma registries shared similar findings. In the UK Severe Asthma Registry (UKSAR), Jackson et al. found that T2-low asthmatics (defined by FeNO < 25 ppb and BEC < 150 cells/μL at registration) had higher body mass index, higher prevalence of depression/anxiety, and higher rate of current smoking and maintenance OCS use. Many T2-low asthmatics had evidence of a historically elevated BEC, and they frequently had prior blood eosinophilia consistent with possible excessive corticosteroid exposure. These subjects probably had T2-high instead of T2-low asthma as they were on corticosteroids which suppressed the T2 biomarkers. T2-high patients (defined by FeNO ≥ 25 ppb and BEC ≥ 150 cells/μL at registration) were more likely to be male, were of older age of symptom onset, were never-smoker, had nasal polyposis and had more severe airflow obstruction.[44] The International Severe Asthma Registry enrolled severe asthma patients from 11 countries. This study categorised subjects according to the likelihood of eosinophilic phenotype using a predefined algorithm based on highest BEC, long-term OCS use, elevated FeNO, nasal polyps and adult-onset asthma. It was found that, among 1,716 patients, 83.8%, 8.3% and 1.6% were identified as most likely eosinophilic, likely eosinophilic and non-eosinophilic phenotypes respectively. Patients with an eosinophilic phenotype showed asthma with a later onset and worse post-bronchodilator % predicted FEV1 than those with a non-eosinophilic phenotype. Patients with non-eosinophilic phenotypes were more likely to be women, have eczema, and to be on anti-IgE therapy and leukotriene receptor antagonists.[45]

THERAPEUTIC OPTIONS BASED ON PHENOTYPING

The main goal of phenotyping severe asthma is to guide personalised management and to differentiate responders from non-responders to the expensive biologic agents.[5,17,36,37,46,49] After phenotyping, further review on disease control and titration of inhaler medications should be considered again.[6] In T2-high asthma, a higher dose of ICS for 3 to 6 months may be considered if the patient is adherent to treatment. Alternative diagnoses sharing the same inflammatory pathway contributing to similar symptoms should be excluded, including aspirin-exacerbated respiratory disease (AERD), allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis and nasal polyposis.[6] In T2-low asthma, the diagnosis, treatment compliance and ongoing exposure to triggers should be thoroughly reviewed. Further investigations, including CT thorax, bronchoscopy and sputum examination, may be considered for alternative or additional diagnoses.[6]

The phenotype-based indication for the biologic agents varies, with omalizumab requiring evidence of allergy, and dupilumab requiring evidence of either eosinophilia or corticosteroid dependence, while others (mepolizumab, reslizumab and benralizumab) requiring evidence of eosinophilia.[6,41,47,48] In general, phenotype-based biological treatment gives favourable treatment benefits by reducing the frequency of asthma exacerbations, lowering the dose of or allowing cessation of OCS, and improving quality of life, asthma control and lung function.[47] Only physicians with experience treating severe uncontrolled asthma should initiate the biological treatment.[49] The lack of user-friendly biomarkers in identifying non-eosinophilic asthma has limited the choice of add-on therapy in this group of patients, which is typically resistant to ICS.[17,50] No biologic options are currently available for non-eosinophilic asthma.[6] Long-acting muscarinic antagonist (LAMA), macrolides at immunomodulatory doses, long-term OCS and bronchial thermoplasty may be considered if the disease remains uncontrolled with traditional therapeutic options.[6] More options may be available when more promising data are available for investigational agents, including anti-IL-17, anti-IL-33 and anti-thymic stromal lymphopoietin.[10,40,47]

Nonetheless, personalised medicine in asthma is not just about phenotyping or checking a panel of biomarkers but also about offering holistic care by treating various asthma-related symptoms. McDonald et al. performed a multidimensional assessment and identified a significant trait burden in severe asthma. By targeting these treatable traits using a personalised-medicine approach, patients benefited from improved health-related quality of life, asthma control and reduced primary care acute visits.[51] This preliminary data hints at the future direction of personalised management of severe asthma.

CONCLUSION

The emphasis on personalised medicine has revolutionised asthma care by benefiting severe asthma patients with appropriate therapeutic care and treatment advice. The therapeutic advances in the past few decades have proved that phenotype-based therapies are essential in treating severe asthma. Emerging data on phenotyping in mild-to-moderate asthma[52,53], long-term safety data of biologics and rapid development of investigational drugs for various asthma phenotypes will revolutionise the treatment paradigm shortly.[47]

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參考資料：1. Bousquet J, et al. Onset of Action of the Fixed Combination Intranasal Azelastine-Fluticasone Propionate in an Allergen Exposure Chamber. *J Allergy Clin Immunol Pract*. 2018;6(5):1726-1732.e6.
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DYMISTA NASAL SPRAY SUMMARY OF PRODUCT INFORMATION. 1. TRADE NAME: DYMISTA NASAL SPRAY **2. PRESENTATION:** Each Dymista nasal spray bottle contains 23 g suspension in 25 ml bottles. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 mcg azelastine) and 50 mcg fluticasone propionate. **3. INDICATIONS:** Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocorticoid is not considered sufficient. **4. DOSAGE:** For nasal use only. Adult and adolescents (12 years and older): one actuation in each nostril twice daily (morning and evening). Children below 12 years: not recommended for use in children below 12 years. Elderly population: no dose adjustment required. No data in patients with renal and hepatic impairment. **5. CONTRAINDICATIONS:** Hypersensitivity to the active substances or to any of the excipients. **6. WARNINGS & PRECAUTIONS:** Systemic effects may occur, particularly at high doses for prolonged periods. Potential systemic effect may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioral effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Caution is advised in patients with severe liver disease given the extensive first pass metabolism of Dymista Nasal Spray and thus higher systemic exposure of intranasal fluticasone propionate. Reduce intranasal fluticasone formulation to the lowest dose at which effective control of symptoms is maintained. Weigh the possible benefit against risk in patients with tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth. Care must be taken in patient transferring from systemic steroid treatment to Dymista Nasal Spray with impaired adrenal function. Visual disturbance may be reported with systemic and topical corticosteroid use. Closely monitor patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts. Growth retardation has been reported in children. Regularly monitor the growth of adolescents receiving prolonged treatment with nasal corticosteroids. Dymista contains benzalkonium chloride, which may cause irritation of the nasal mucosa and bronchospasm. **7. INTERACTIONS:** Avoid concomitant use with ritonavir and other CYP3A4 inhibitors including cobicistat-containing products unless the benefit outweighs the increased risk of systemic corticosteroid side effects. Care is advised in concomitant use with potent CYP3A4 inhibitors (e.g. ketoconazole), sedative and central nervous medication. **8. PREGNANCY AND LACTATION:** No or limited data in pregnant women. Unknown if the ingredients/metabolites are excreted in human breast milk. Used only if the potential benefit justifies the potential risk. **9. SIDE EFFECTS:** Epistaxis, Headache, dysgeusia, unpleasant smell. Reference: HK PI (Aug 2020) Date of preparation: OCT2021 Identifier number: DYM1021

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REFERENCES: 1. Trelegy Hong Kong Prescribing Information, GDS05, Nov 2018 2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438–446. 3. Lipson DA et al. N Engl J Med 2018; 378:1671–1680.

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SAFETY INFORMATION

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- 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

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Elderly patients (>65 years), patients with renal impairment or hepatic impairment: No dose adjustment. Trelegy Ellipta should be used with caution in patients with moderate to severe hepatic impairment. **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 beta$_2$-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 beta$_2$-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 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 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 beta$_2$-adrenergic agonists Co-administration of *Trelegy Ellipta* with other long-acting muscarinic antagonists or long-acting beta$_2$-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, bronchitis,sinusitis, candidiasis of mouth and throat, urinary tract infection, constipation, oropharyngeal pain, rhinitis, influenza, nasopharyngitis, headache, cough, arthralgia, back pain; Uncommon:, viral respiratory tract infection, supraventricular tachyarrhythmia, tachycardia, atrial fibrillation, oropharyngeal pain, fractures, dysphonia, dry mouth. **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* Prescribing Information, Hong Kong (HK122018, GDS05/EMA20181121). Please read the full prescribing information prior to administration. Full prescribing information is available on request from GlaxoSmithKline Ltd, 23/F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong. For adverse events reporting, please call GlaxoSmithKline Limited at (852) 3189 8989 (Hong Kong) or email to HK Adverse Event mailbox: HKAdverseEvent@gsk.com

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Severe Asthma:Phenotyping and Its Implication for Treatment" by Dr Ka-pang CHAN and Dr Fanny WS KO 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 June 2022. 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. **Disease phenotyping is important in the management of severe asthma.**
2. **Severe asthma is defined as asthma that is uncontrolled despite adherence with maximal optimised therapy (high dose inhaled corticosteroids plus a second controller) and treatment of contributory factors, or that worsens when high dose treatment is decreased.**
3. **Increasing the dose of inhaled corticosteroids alone is adequate when seeing patients with uncontrolled asthma.**
4. **The basic principle of phenotyping is to identify whether asthma follows a T2-high or T2-low inflammatory pathway.**
5. **Blood neutrophil count is the most important phenotyping parameter for asthma.**
6. **Fractional exhaled nitric oxide (FeNO) of more than 50 ppb in adults suggests the presence of T2-high inflammation, whereas FeNO of less than 25 ppb suggests a T2-low process.**
7. **Allergic eosinophilic asthma is characterised by early-onset atopic diseases, high IgE levels and the presence of aeroallergen allergy.**
8. **Non-allergic eosinophilic asthma is often young-onset, without nasal polyposis and salicylate sensitivity, lower blood and lung eosinophil concentrations; the IgE is frequently elevated.**
9. **Non-eosinophilic asthma lacks T2-driven inflammation but has a neutrophilic predominance in the airways. It is often associated with smoking, obesity, occupational exposures, and a poor clinical response to escalating corticosteroid therapy.**
10. **Biologic therapies (mepolizumab, reslizumab, benralizumab and omalizumab) are indicated for patients with non-eosinophilic asthma.**

ANSWER SHEET FOR JUNE 2022

Please return the completed answer sheet to the Federation Secretariat on or before 30 June 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Severe Asthma: Phenotyping and Its Implication for Treatment

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to May 2022 Issue

Exploration of the New Parent Education in Mental Health Programme (PEMH) at Hong Kong Primary Schools - Interim Results

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

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Use of Biologics for Severe Eosinophilic Asthma

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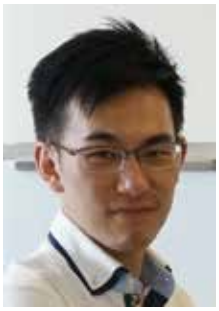


Dr Wang-chun KWOK Dr David CL LAM

INTRODUCTION

According to the 2014 American Thoracic Society (ATS) classification,[1] the clinical condition of severe asthma is defined as "patients who require high dose inhaled or near continuous oral glucocorticoid treatment to maintain asthma control". In patients with severe asthma, it is important to define a definitive clinical phenotype which can guide clinical management.

Among the 4,990 patients in the 2020 International Severe Asthma Registry, 34.9% were at GINA Step 5 and 57.2% had poorly controlled disease. In this registry, 48.5% of the patients had a blood eosinophil count of more than 300 cells/μL, and 56.9% of the patients had fractional exhaled nitric oxide (Fe_{NO}) concentrations of more than or equal to 25 parts per billion (ppb).[2] In recent decades, long-term oral corticosteroids have been largely replaced by various types of biologics for the management of severe eosinophilic asthma, which is defined by patients with severe asthma that had inflammation driven by eosinophilic inflammation and have blood eosinophil level above 150 cells/μL[29].

Anti-IgE THERAPY

Omalizumab is a recombinant humanised IgG1 monoclonal antibody that binds circulating IgE, forming immune complexes that are subsequently cleared by the hepatic reticuloendothelial system. This binding inhibits the attachment of IgE to IgE-receptors on mast cells, basophils, and other cell types, thereby reducing surface IgE receptor levels and the activation of these cells upon allergen exposure.[30]

Omalizumab is approved by the US Food and Drug Administration (FDA) in the United States for use in patients who are six years of age or older, with moderate-to-severe persistent allergic asthma, as manifested by a serum IgE level of 30 to 700 IU/mL, positive allergen skin or specific IgE tests to a perennial allergen, and suboptimal symptom control with inhaled glucocorticoid treatment.[3-5] Omalizumab is administered by subcutaneous injection. The dose is determined by the body weight and the levels of serum IgE (0.016 mg/kg per IU/mL of IgE per month). A dose of 150 to 375 mg is injected subcutaneously every two to four weeks to achieve the monthly target. No more than 150 mg should be administered at a single injection site to prevent local reactions.[31]

Omalizumab was shown to achieve 25% reduction in the rate of asthma exacerbations compared with placebo among patients with severe asthma that have poor symptom control on fluticasone 1,000 mcg/d and a long-acting beta-2-agonist (LABA).[6] Type 2 lymphocyte-associated inflammatory biomarkers (exhaled nitric oxide, peripheral blood eosinophils, serum periostin) were suggested to predict response to omalizumab.[7]

Apart from asthma, omalizumab is also effective for the treatment of chronic urticaria that is refractory to antihistamine therapy. It is also reported to be helpful in the management of food allergy, nasal polyposis, idiopathic anaphylaxis, allergic rhinitis, venom hypersensitivity and atopic dermatitis.[8-10]

Anaphylaxis occurs in approximately 1 to 2 per 1,000 patients and can develop after any dose, including the first one; the onset of anaphylaxis can be delayed, and the clinical course protracted. Other reported adverse events include injection site reaction, serum sickness and urticaria (2%).

Anti-IL-5 THERAPY

Interleukin (IL)-5 is a pro-eosinophilic cytokine and a mediator of eosinophil hematopoiesis and contributes to eosinophilic inflammation in the airways. Mepolizumab and reslizumab are anti-IL-5 monoclonal antibodies while benralizumab is an anti-IL-5 receptor alpha antibody.

a. Mepolizumab

Mepolizumab is approved by the FDA and recommended by the National Institute for Health and Care Excellence (NICE) for use as add-on, maintenance treatment of severe asthma in patients who are aged 12 years or older and have an eosinophilic phenotype with absolute blood eosinophil count ≥ 150/μL. Mepolizumab is administered subcutaneously at a dose of 100 mg every four weeks.

Mepolizumab was shown to reduce exacerbations in patients with eosinophilic asthma (Incidence rate ratio 0.49; 95% CI 0.38-0.66; approximately 592 fewer exacerbations per 1,000 patients per year).[11] Mepolizumab was also reported to improve asthma control and quality of life, but did not meet the minimum threshold of clinically important difference. In the SteroId ReductIon with mepolizUmab Study

(SIRIUS), the likelihood of a reduction in the oral glucocorticoid dose was 2.39 times greater in the mepolizumab group (95% CI 1.25-4.56) and the mean reduction from baseline was 50% compared with no reduction in the placebo group.[32]

Apart from asthma, mepolizumab is also beneficial in glucocorticoid-sensitive hyper-eosinophilic syndromes (HES), including idiopathic HES, lymphocytic variants of HES (L-HES), and HES/eosinophilic granulomatosis with polyangiitis (EGPA) overlap, EGPA and chronic rhinosinusitis with nasal polyp.[12-14] Hypersensitivity reactions have been reported with mepolizumab. *Herpes zoster* infection has also been reported in a small number of patients receiving mepolizumab.

b. Benralizumab

Benralizumab is approved by the FDA as add-on therapy in patients (≥ 12 years of age) with severe asthma and an eosinophilic phenotype with blood eosinophil count of ≥ 150 cells/μL. Benralizumab depletes IL-5 receptor-bearing cells (eosinophils and basophils) via enhanced antibody-dependent cytolysis and blockage of IL-5 binding to its receptor.[15-17] Benralizumab is given subcutaneously, 30 mg every four weeks for the first three doses, and then 30 mg every eight weeks.

In the multi-centre SIROCCO trial, benralizumab reduced the exacerbation rate in every-four-week and every-eight-week groups (Rate ratio [RR] 0.55, 95% CI 0.42-0.71, and RR 0.49, 95% CI 0.37-0.64, respectively). Benralizumab also improved pre-bronchodilator FEV_1 and asthma symptom scores in patients with blood eosinophil count of ≥ 300 cells/μL. In the multi-centre CALIMA trial, compared with placebo, the annual exacerbation rate among those with a peripheral eosinophil count ≥ 300 cells/μL and on high-dose inhaled glucocorticoids was decreased in the "every-four-week" benralizumab group (RR 0.64, 95% CI 0.49-0.85) and in the "every-eight-week" group (RR 0.72, 95% CI 0.54-0.95). f=In the multicentre ANDHI trial, benralizumab decreased annual asthma exacerbations compared with placebo (RR 0.51, 95% CI 0.39-0.65).[18]

In the 28-week multi-centre trial (ZONDA), at the end of 28 weeks, the oral glucocorticoid dose was decreased by 75% from baseline in the benralizumab groups, compared with 25% in the placebo group. The odds of a reduction in the oral glucocorticoid dose with benralizumab every eight weeks were 4.12 times (95% CI 2.22-7.63) that of placebo. The annualised exacerbation rates were lower with benralizumab; the marginal rates were 0.83 for benralizumab every four weeks, 0.54 for benralizumab every eight weeks, and 1.83 for placebo. FEV_1 was not significantly different between the groups at 28 weeks.[19]

The most common adverse events were headache and pharyngitis. Hypersensitivity reactions (anaphylaxis, angioedema, urticaria) occurred in approximately 3 percent of subjects, usually within a few hours, but occasionally after a few days. The occurrence of hypersensitivity reaction is a contraindication to further use of benralizumab.[17,20]

c. Reslizumab

Reslizumab is approved by the FDA as add-on, maintenance therapy for severe asthma in patients who are aged 18 or older and have an eosinophilic phenotype, which was defined as having a blood eosinophil count of 400/μL or greater. It is administered at a dose of 3 mg/kg by intravenous infusion over 20 to 50 minutes.

Reslizumab was shown to reduce exacerbations in patients with eosinophilic asthma (Incidence rate ratio 0.46, 95% CI 0.37-0.58; approximately 972 fewer exacerbations per 1,000 patients/year) compared with standard of care.[11] Reslizumab was also demonstrated to improve FEV_1 compared with placebo by week 4, and the improvement persisted through to week 52 (0.22 L versus 0.12 L). It also resulted in a significant improvement in quality of life and in asthma symptoms, based on the Asthma Symptom Utility Index and the Asthma Control Questionnaire-7.[21] Reslizumab also reduced sputum eosinophil level.[22] The reported adverse events from reslizumab include myalgia, oropharyngeal pain, a transient increase in creatine phosphokinase, and rarely anaphylaxis.

Anti-lL-4 RECEPTOR ALPHA SUBUNIT ANTIBODY

Dupilumab is a human monoclonal antibody that binds to the alpha subunit of IL-4 receptor. Through the blockade of this receptor, dupilumab inhibits the activity of both IL-4 and IL-13, which are type 2 cytokines that play a key role in allergy and asthma. Dupilumab is approved by the FDA for the treatment of moderate-to-severe, eosinophilic asthma with peripheral blood eosinophils ≥ 150/μL in patients who are six years of age and older. The recommended dose of dupilumab is an initial 400 mg, followed by 200 mg given every other week or an initial dose of 600 mg followed by 300 mg given every other week. The higher dose is suggested for patients with oral glucocorticoid-dependent asthma or comorbid moderate-to-severe atopic dermatitis. Pre-existing helminth infections should be treated prior to initiation of dupilumab.

In a multi-centre trial, the annualised rate of severe exacerbations decreased by approximately one-half in the dupilumab groups. The annualised rate in the dupilumab 200 mg group was 0.46 (95% CI 0.39-0.53), compared with 0.87 (95% CI 0.72-1.05) in the placebo group. FEV_1 increased significantly in the dupilumab 200 mg group, which was 0.14 L greater than that in the placebo group. Therapeutic effects appeared to be greater among participants with a baseline blood eosinophil count of 300/μL. Among patients with a baseline blood eosinophil count of 150 to 299/μL, the exacerbation rate was also lower with dupilumab compared with placebo. Greater reductions in exacerbation rate correlated with higher fraction of exhaled nitric oxide (FENO) levels.[23] Dupilumab can also provide benefits in terms of steroid sparing. The oral glucocorticoid dose decreased by 70% in the dupilumab group and by 42% in the placebo group. Eighty percent of dupilumab-treated patients versus 50% of placebo-treated patients had a dose reduction of at least 50 percent.[24]

Table 1: Biologics for severe eosinophilic asthma (Adapted from www.uptodate.com)

Agents and their targets	Patient eligibility	Route	Dose	Dosing interval	Adverse effects	Clinical benefits beyond asthma
For patients with elevated serum IgE and sensitivity to perennial allergens						
Omalizumab (anti-IgE)	Serum IgE 30 to 700 IU/mL in United States; 30 to 1,500 IU/mL in Europe	SC	Based on weight and serum IgE levels Doses ≥ 225 mg need to be divided over > 1 injection sites Maximal dose: 375 mg every two weeks in United States; 600 mg every two weeks in Europe	Two to four weeks depending on IgE level and body weight	• Local injection site reaction (severe 12%), usually within 1 hour • Thromboembolic disease ≤ 3% • Anaphylaxis, immediate or delayed < 1% • Antibody development (< 1%)	• Chronic urticaria • Food allergy • Nasal polyposis • Idiopathic anaphylaxis • Allergic rhinitis • Venom hypersensitivity • Atopic dermatitis
For patients with eosinophilic phenotype						
Mepolizumab (anti-IL-5)	Peripheral blood eosinophils ≥ 150/μL	SC	100 mg$^{\Delta}$	Four weeks	• Headache (19%) • Local injection site reaction (8 to 15%) • Anaphylaxis: Immediate or delayed < 1% • Human anti-human neutralising antibody (< 1%) • Herpes zoster (< 1%): Administration of zoster vaccine is suggested prior to initiation.	• Glucocorticoid-sensitive hyper-eosinophilic syndromes (HES), including idiopathic HES, lymphocytic variants of HES (L-HES), and HES/eosinophilic granulomatosis with polyangiitis (EGPA) overlap • EGPA • Chronic rhinosinusitis with nasal polyp
Benralizumab (anti-IL-5 receptor alpha)	Peripheral blood eosinophils ≥ 150/μL	SC	30 mg	Four weeks for first 3 doses, then eight weeks	• Human anti-human antibody development (13%; neutralising 12%) • Headache 8% • Fever 3% • Hypersensitivity (anaphylaxis, angioedema, urticaria; 3%): typically within hours of injection but can be delayed (3%)	
Dupilumab (anti-IL-4 receptor subunit alpha)$^{\Diamond}$	Peripheral blood eosinophils ≥ 150/μL	SC	First week, 400 mg once (given as two 200 mg injections), then 200 mg every two weeks	Two weeks	• Human anti-human antibody development in patients receiving the 300 mg dose every two weeks for 52 weeks (6%; 2% with neutralising antibodies) and in patients taking 200 mg dose every 2 weeks for 52 weeks (9%; 4% with neutralising antibodies) • Transient eosinophilia (4%); over 3,000 cells/mL (1.2%) • Anaphylaxis and other hypersensitivity reactions (< 1%) • Injection site reactions, conjunctivitis, keratitis, oral and other herpes simplex viral infections	• Severe atopic dermatitis • Chronic rhinosinusitis with nasal polyp
			First week, 600 mg once (given as two 300 mg injections), then 300 mg every two weeks$^{\Diamond}$	Two weeks		
Reslizumab (anti-IL-5)	Peripheral blood eosinophils ≥ 400/μL	IV	3 mg/kg	4 weeks	• Human anti-human antibody development (5%) • Anaphylaxis 0.3% during infusion or within 30 minutes after infusion; may occur as early as the second dose or can be delayed • Transient increase in creatine phosphokinase (20%)	

Abbreviations: Subcutaneous: SC, Intravenous: IV

Dupilumab is also approved in the treatment of moderate to severe atopic dermatitis not adequately controlled with topical prescription therapies[25,26] and chronic rhinosinusitis with nasal polyp.[27] Adverse effects with dupilumab include injection site reactions (15%) and transient eosinophilia of over 3,000 cells/μL in 15 patients (1.2%). Of these patients, seven discontinued therapy due to eosinophilia, and four had associated symptoms (e.g, fever, myalgia, cough, dyspnea). Anti-drug antibody responses were noted in 2 to 5 percent of dupilumab-treated patients versus 1 to 5 % in the placebo group; such anti-drug antibody responses did not appear to affect efficacy. Table 1 summarises the currently approved biologics for severe eosinophilic asthma.

BIOLOGICS FOR BOTH EOSINOPHILIC AND NON-EOSINOPHILIC ASTHMA

Tezepelumab

Tezepelumab is a human monoclonal antibody (IgG2λ) that binds specifically to thymic stromal lymphopoietin (TSLP), blocking it from interacting with its heterodimeric receptor. In a phase 3, multi-centre, randomised, double-blind, placebo-controlled trial, patients were randomly assigned to receive tezepelumab (210 mg) or placebo subcutaneously every four weeks for 52 weeks. The annualised rate of asthma exacerbations was 0.93 (95% CI, 0.80 to 1.07) with tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P < 0.001). In patients with a blood eosinophil count of less than 300 cells/μL, the annualised rate was 1.02 (95% CI, 0.84 to 1.23) with tezepelumab and 1.73 (95% CI, 1.46 to 2.05) with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P < 0.001). At week 52, improvements were greater with tezepelumab than with placebo with respect to pre-bronchodilator FEV_1 (0.23 vs. 0.09 litres; difference, 0.13 litres; 95% CI, 0.08 to 0.18; P < 0.001) and scores on the ACQ-6 (-1.55 vs -1.22; difference, -0.33; 95% CI, -0.46 to -0.20; P < 0.001), AQLQ (1.49 vs 1.15; difference, 0.34; 95% CI, 0.20 to 0.47; P < 0.001), and Asthma Symptom Diary (-0.71 vs -0.59; difference, -0.12; 95% CI, -0.19 to -0.04; P = 0.002). Injection-site reactions occurred in 3.6% of patients in the tezepelumab group and in 2.6% of those in placebo group. No treatment-related anaphylactic reactions or cases of Guillain-Barré syndrome were reported. At baseline or after, 4.9% of patients in tezepelumab group and 8.3% of those in the placebo group were positive for anti-drug antibodies (Table S10). Neutralising antibodies were detected in one patient in each group.[28]

CONCLUSION

The development of biologics in asthma, targeting different phenotypes in eosinophilic inflammation, has revolutionised the management of severe uncontrolled eosinophilic asthma. Long-term steroids have largely been replaced with the introduction of biologics. The development of biologics focusing on upstream targets may also benefit patients with non-Th2 driven asthma.

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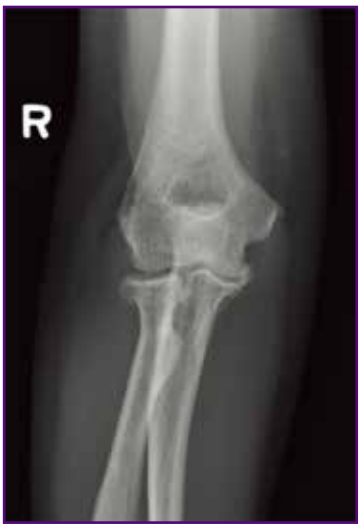
Radiology Quiz

Dr Derek LH CHAN

MBBS, FRCR

Dr Derek LH CHAN



Questions

A 72-year-old woman attends the Accident and Emergency Department complaining of right elbow pain after a fall onto an outstretched hand. Radiographs of the right elbow were performed.

1. What do the radiographs show?
2. What is the usual management for this pathology?

(See P.40 for answers)

Neutrophilic Asthma: the Non-Type 2 / Non-T2 or T2-low Asthma

Dr Yiu-cheong YEUNG

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INTRODUCTION

Asthma is a heterogeneous disease characterised by chronic airway inflammation. The main treatment includes inhaled corticosteroids (ICS), inhaled corticosteroids plus long-acting β2-adrenergic agonists (ICS+LABA) and long-acting muscarinic antagonist (LAMA) aiming at controlling the airway inflammation.[1] Most patients with asthma have a mild or moderate disease that potentially can be controlled by the above treatment.[2] However, a subset of asthma patients experience severe and persistent symptoms despite appropriate therapies. Surveys around the world including the Asia Pacific region and Hong Kong showed evidence that despite the use of current therapies, some patients have poorly controlled symptoms and experience frequent exacerbation.[3]

According to the 2014 guidelines of the European Respiratory Society and American Thoracic Society, severe asthma is defined as asthma that requires treatment with high-dose ICS as well as a second controller, including the possible use of systemic corticosteroids; and symptoms can either be controlled or uncontrolled with such therapy.[4] The Global Initiative for Asthma (GINA) published an updated document on the management of severe asthma in 2021, in which severe asthma is defined as asthma that is uncontrolled despite adherence with maximal optimised high dose ICS-LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased.[2] Severe asthma represents 3.7% of the total asthma population and is known to inflict a high burden of disease with frequent asthma exacerbations and/or progressive lung function decline resulting in excessive utilisation of health care resources.[2,4]

It is important to recognise that severe asthma represents a heterogeneous group of multiple phenotypes. Treatment should be tailored according to the underlying pathophysiologic mechanism.[1] Asthma can broadly be classified into T2-asthma and non-T2 asthma. T2-asthma (T2-high) asthma is generally known to be associated with eosinophilic airway inflammation. The T2-asthma is a better defined group and can be identified using available biomarkers, namely fraction of exhaled nitric oxide (FeNO), blood eosinophil count, serum IgE level and sputum eosinophil percentage. This set of characteristics has facilitated relevant research and the booming of biologics for T2- asthma approved in the market. On the contrary, non-Type 2 asthma or non-T2 asthma (also known as T2-low asthma) is less well defined and comprises a diverse group, whose disease is driven by less well-defined pathobiologic mechanism.

Non-T2 asthma is an umbrella term and may include neutrophilic, pauci-granulocytic and mixed types according to sputum quantitative cytometry.[5] In adopting sputum cytometry as the method of classification, there remain controversies on (1) what the cut-off value of sputum neutrophil should be, (2) variability of sputum neutrophilia over time, (3) how the changes in sputum neutrophil could impact the treatment plan, and (4) environmental factors such as allergen exposures, seasonal changes and airway microbiology.[6]

THE MANAGEMENT OF NON-TYPE 2 ASTHMA

When managing a patient with severe asthma, the GINA guidelines recommend assessing the severe asthma phenotype, particularly looking for the feature of T2- inflammation with currently available biomarkers (FeNO, blood eosinophil count, serum IgE level and sputum eosinophil percentage) and suggest add-on Type 2 biologics if appropriate and available.[1]

For non-T2 asthma, active research has been done to develop novel pharmacological agents. The studies on C-X-C motif chemokine receptor 2 antagonist, anti-TNF-alpha, anti-IL-1[7], anti-IL1, anti-IL[6], IFN, KIT inhibitor, 5-lipooxygenase-activating protein inhibitor, LC28-0126, IL-23 were all disappointing.[7] Non T2-asthma represents one of the greatest challenges in the field of asthma management, given the lack of specific biomarkers to identify it and the lack of effective immune modulators to treat this.

The management of non-T2 asthma includes pharmacological and non-pharmacological treatment. For the patient with no evidence of type 2 airway inflammation, add-on treatment options included (if available and not already tried): LAMA, low dose azithromycin, anti-IL-4R, anti-thymic stromal lymphopoietin (anti-TSLP) and add-on low dose oral corticosteroids. Non-pharmacological treatments that should be considered include smoking cessation, weight reduction in obesity and bronchial thermoplasty.[1]

Here we will review the use of macrolide and bronchial thermoplasty in severe asthma.

MACROLIDE (AZITHROMYCIN) IN THE MANAGEMENT OF SEVERE ASTHMA

Macrolide's role in respiratory medicine has included the treatment of the patient with bronchiectasis, cystic fibrois, diffuse panbronchiolitis, COPD and asthma. Azithromycin is a macrolide antibiotic that inhibits bacterial protein synthesis and carries anti-inflammatory properties. The two major studies on the efficacy and safety of long term use of azithromycin in severe asthma with promising results were AZISAST and AMAZES trials[8,9].

In the AZISAST trial, a randomised double-blind placebo-controlled parallel-group multicentre study, the authors randomised 109 exacerbation-prone severe asthmatics to low-dose azithromycin (250 mg three times per week) vs placebo for six months. In a pre-defined subgroup of severe non-eosinophilic asthma, the azithromycin group was significantly associated with fewer severe asthma exacerbations during the 6-month period (estimated primary end-point rate ratio for azithromycin vs placebo 0.43, p=0.013; estimated severe exacerbation rate ratio for azithromycin vs placebo 0.42, p=0.05).[8]

In a larger randomised, double-blind, placebo-control trial (AMAZES), 420 adults with moderate-to-severe persistently symptomatic asthma were recruited and randomised (1:1) with oral azithromycin (500 mg daily three times per week) vs placebo for 48 weeks. The authors demonstrated that azithromycin significantly reduced 41% of the incidence of total (moderate to severe) exacerbations (incidence rate ratio 0.59, p< 0.0001). The AMAZES study also showed an improvement in asthma-related quality of life (Asthma Quality of Life Questionnaire, AQLQ score). Moreover, the benefits of azithromycin were demonstrated in both eosinophilic and non-eosinophilic asthma phenotypes. Furthermore, the study also demonstrated safety as there were no significant adverse effects such as hearing loss or prolonged QTc in subjects receiving azithromycin.[9]

Position of azithromycin in the latest international asthma guidelines:

- Management of severe asthma (ERS/ATS 2020): a trial of macrolide treatment is suggested to reduce asthma exacerbations in adult asthma subjects on GINA/NAEPP step 5 therapy that remains persistently symptomatic or controlled (conditional recommendation, low quality of evidence). The guidelines added the remarks that the recommendation is based on the need to avoid exacerbations and to reduce OCS. The benefits and safety of using macrolides for asthma beyond one year has not been determined.[29]

- GINA 2022: if there is no evidence of type 2 inflammation or if there is evidence of type 2 inflammation but biologics are not available or affordable, the GINA guidelines suggest considering a trial of non-biologic add-on treatment like azithromycin if not already tried (add-on treatment options included: Long-acting muscarinic antagonist; leukotriene modifier; low dose azithromycin for adult, but with azithromycin due consideration is needed for potential for antibiotic resistance). Add-on azithromycin (three times a week) can be considered after specialist referral. In term of precaution, GINA suggests before considering add-on azithromycin, sputum should be checked for atypical mycobacteria, ECG should be checked for long QTc (and re-checked after a month on treatment), and the risk of increasing antimicrobial resistance should be considered. Treatment for at least six months is suggested, as a clear benefit was not seen by three months in the clinical trials.[1]

BRONCHIAL THERMOPLASTY IN THE MANAGEMENT OF SEVERE ASTHMA

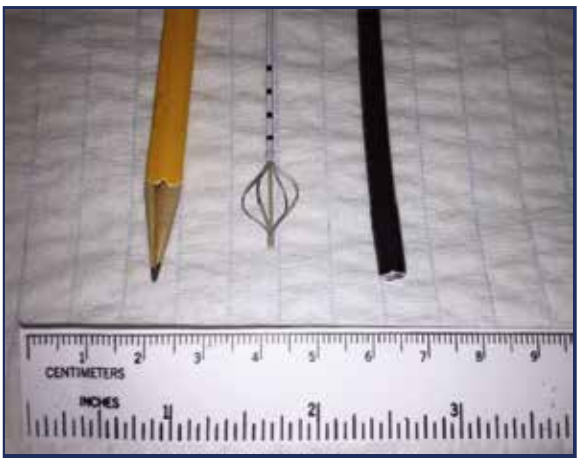

Fig. 1: The distal end of the bronchial thermoplasty catheter was shown, next to the bronchoscope and a pencil (Personal collection)

Airway smooth muscle (ASM) plays a critical structural and immunomodulatory role in the airway and contributes to exacerbations and chronic airway remodelling in asthma.[10] In 2010, the US FDA gave premarket approval for the Alair® bronchial thermoplasty (BT) system as a treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with ICS and LABA.[11] Bronchial thermoplasty is a non-pharmacological intervention that applies controlled delivery of radiofrequency (RF) thermal energy to the airways via the Alair catheter electrode, with the aim of reducing the amount of airway smooth muscle and improving asthma control. The RF electrical energy is systemically applied to airways between 3 and 10 mm in diameter throughout the tracheobronchial tree, in three separate bronchoscopic sessions of 4 weeks apart.[12]

Here we will provide a quick review of the recent literature starting from the result of three major randomised control trials on BT leading to the FDA approval. The efficacy on short and longer terms and its safety will then be reviewed. It is through real life case series of the registry data in North America, the UK, and Australia that provide not only real life data but also the efficacy and safety profile of BT in the more severe group of asthma patients.

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References: 1. O'Byrne PM et al. N Engl J Med 2018; 378: 1865-76. **2.** Bateman ED et al. N Engl J Med 2018; 378: 1877-87. **3.** Beasley R et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1901963. **4.** Hardy J et al. Lancet 2019; Published online Aug 23, 2019; http://dx.doi.org/10.1016/S0140-6736(19)31948-8. **5.** Kuna P et al. Int J Clin Pract 2007 (May); 61(5): 725 – 36. **6.** Bousquet J et al. Respir Med 2007; 101: 2437 – 46. **7.** Sobieraj DM et al. JAMA 2018; doi: 10.1001/jama.2018.2769. **8.** Symbicort Hong Kong Package Insert. Feb 2021.

Presentation: Budesonide/Formoterol Turbuhaler. **Indications:** In adults and adolescents (12 years and older), for the treatment of asthma, to achieve overall asthma control, including the relief of symptoms and the reduction of the risk of exacerbations. Symptomatic treatment of moderate to severe COPD in adults. **Dosage:** **Asthma** ***1) Symbicort anti-inflammatory reliever therapy (patients with mild disease) 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1 inhalations as needed in response to symptoms. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***2) Symbicort maintenance and reliever therapy*** *Adult & Adolescent ≥ 12yr:* Patients should take 1 inhalation of Symbicort Turbuhaler 160/4.5 mcg as needed in response to symptoms to control asthma. If symptoms persist after a few minutes, 1 additional inhalation should be taken. No more than 6 inhalations should be taken on any single occasion. Recommend maintenance dose is 1 inhalation b.d. and some may need 2 inhalations b.d.. A total daily dose of more than 8 inhalations is normally not needed, however a total daily dose of up to 12 inhalations can be used temporarily. ***3) Symbicort maintenance therapy 160/4.5 mcg Turbuhaler*** *Adult & Adolescent ≥ 12yr:* 1-2 inhalations b.d.. Max daily dose is 4 inhalations. **COPD** ***160/4.5 mcg Turbuhaler*** *Adult:* 2 inhalations b.d.. Max daily dose is 4 inhalations. **Contraindications:** Hypersensitivity to budesonide, formoterol or lactose. **Precautions:** Should be used for the shortest duration of time required to achieve control of asthma symptoms. Should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications. Not be used to initiate treatment with inhaled steroids in patients being transferred from oral steroids. It is recommended that the maintenance dose be tapered when long-term treatment is discontinued. Potential systemic effects of ICS, HPA axis suppression and adrenal insufficiency, bone density, growth, visual disturbance, infections/tuberculosis, sensitivity to sympathomimetic amines, cardiovascular disorders, hypokalaemia, diabetes, pneumonia, lactose, pregnancy & lactation. Not recommended for children below 12 years of age. Incidence of candidiasis can be minimized by having patients rinse their mouth out with water after inhaling their maintenance dose. **Interactions:** CYP3A4 inhibitors, beta-receptor blocking agents, other sympathomimetic agents, Xanthine derivatives, mineralocorticosteroids and diuretics, Monoamine oxidase inhibitors, tricyclic antidepressants, quinidine, disopyramide, procainamide, phenothiazines and antihistamines. **Undesirable effects:** Palpitations, Candida infections in the oropharynx, headache, tremor, mild irritation in the throat, coughing, hoarseness. **Full local prescribing information is available upon request.** API.HK.SYM.0721

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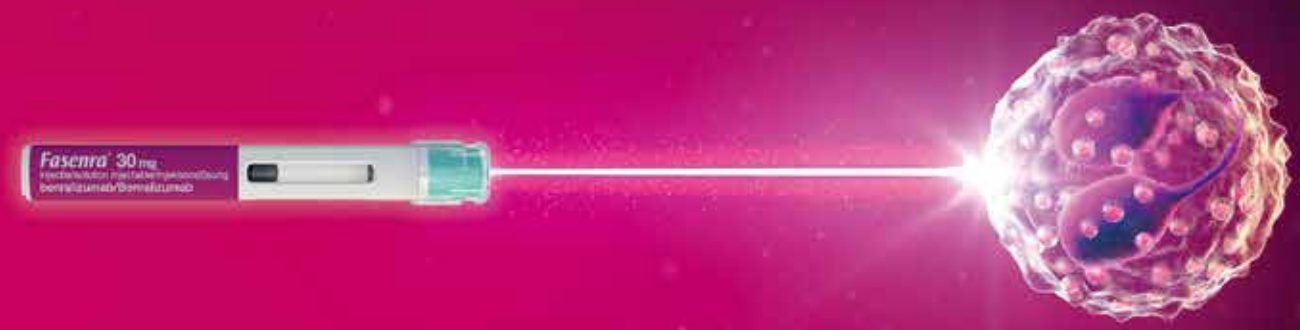
AIMS FOR ZERO



74% of patients had ZERO exacerbations in Year 2 *[2]

Sustained reductions in exacerbations through Year 5 with ZERO new safety signals ^[3]

Up to 62% of patients reduced OCS to ZERO ‡[2]

Presentation: Benralizumab 30 mg solution for injection in pre-filled pen. **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.FAS.0521

References: 1. Fasenra Pen Hong Kong Prescribing Information, May 2021. **2.** Data on File: AstraZeneca 2021. REF-101714. **3.** Bourdin A, et al. Oral presentation at ATS 2021 International Conference, May 14-19, 2021. ATS Website: https://conference.thoracic.org/program/abstract-search.php?sid=P5837. Accessed July 2021. **4.** Busse WW, et al. Lancet Respir Med. 2019;7(1):46-59. **5.** Menzies-Gow A, et al. ERJ Open Res. 2019;5:00009-2019. https://doi-org/10.1183/23120541.00009-2019.

* BORA: Patients from predecessor trials SIROCCO and CALIMA who continued on Q8W dosing during the 56-week evaluation period in the safety extension trial. Patients had blood eosinophils ≥ 300 cell/μL at baseline. [4]
^ MELTEMI: Patients from predecessor trial BORA, a 56-week safety extension trial, who continued on Q4W or Q8W dosing during a 3-year safety evaluation period. Patients had blood eosinophils ≥300 cells/μL at baseline. All analyses were descriptive. [3]
‡ PONENTE: This is an open-label steroid-sparing study. Patients with average daily dose equivalent to ≥5 mg of prednisone for the last 3 months before study entry. Patients had blood eosinophils ≥150 cells/μL at enrolment or ≥300 cells/μL in the past 12 months. [5]

OCS = oral corticosteroid; Q4W = every 4 weeks; Q8W = every 8 weeks.

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HK-5831 26/08/2021

(1) BT: Clinical efficacy and safety in randomisation control trials

The three randomised control trials (RCT) were published from 2007-2010 and provided evidence of clinical efficacy, along with patient selection criteria and the safety profile of BT (Table 1).[13-15] The first RCT is the Asthma Intervention Research (AIR) study, an unblinded randomised trial which recruited 112 patients with moderate or severe persistent asthma. It demonstrated a reduction in the mild exacerbation rate when compared with baseline, with an enhanced asthma-related quality of life with BT. There were also improvements in the Asthma Control Questionnaire (ACQ) score, morning peak expiratory flow and symptom scores when compared with controls.[13] The second RCT is the Research in Severe Asthma (RISA) study, which is primarily a safety trial, with 32 severe asthma patients analysed for BT safety and efficacy. Despite a transient increase in asthma symptoms during the treatment, this study showed a significant improvement in quality of life (AQLQ), asthma control (ACQ), rescue medication use, and pre-bronchodilator FEV1 percentage predicted in BT-treated subjects versus controls.[14] The third RCT is the Asthma Intervention Research study 2 (AIR2), the largest study of all three studies. The AIR2 trial was the first and only RCT to date to include a sham-procedure control arm. Two hundred ninety-seven (297) patients were randomised in a 2:1 ratio to undergo either BT or an identical bronchoscopic procedure without the delivery of RF energy (sham control). Improvements were found in the Asthma Quality of Life Questionnaire (AQLQ) scores in both the intervention and sham control arms but superior improvements were found in the intervention arm. Furthermore, the secondary endpoints showed there was a reduction in severe exacerbations, emergency department visits, and days missed from school/work in the BT Group.[15]

Each of the trials had a measure of poor asthma control in the inclusion criteria to ensure that only patients with uncontrolled asthma were enrolled (Table 1). Patients with more airway obstruction were enrolled in the RISA trial (baseline pre-bronchodilator FEV1 > 50% in RISA, and > 60% in AIR and AIR2 trials).

The extension studies were enrolled from patients from each of these randomised controlled trials and these patients were followed for five years. These extension studies have demonstrated the long-term safety of BT with the stability of the FEV1 on follow-up.[16-18] The AIR2 extension study has shown durable improvements in exacerbation rates and emergency department visits during the five years after BT.[15]

Recently, the BT10+ study (BT at 10 years' follow-up or beyond) suggests that efficacy of bronchial thermoplasty is sustained over 10 years.[19] Of the 429 subjects enrolled in the previous BT RCT studies (AIR, RISA, AIR2), 192 subjects had a follow-up of > 10 years (10.6-15.8 years, median 12.1 years) post-treatment at 16 centres. Rates for hospitalisations, emergency visits and side effects for BT subjects from the year prior to BT to the year prior to the BT 10+ visit were captured. Compared with 12-months prior to BT, a sustained reduction in the number of severe exacerbations per participant, emergency departments visit and hospital admission for asthma were observed at the 10+ visits. The BT10+ study also showed that asthma-related quality of life improved by 12 weeks after BT and this improvement was sustained for 10 years or more after treatment. Spirometry results were comparable between Years 1, 5, and 10+ for all groups. The result of BT10+ study suggests that the efficacy of BT is sustained over 10 years.

For safety issues, BT is associated with short-term increases in asthma-related symptoms and hospital admissions for asthma during the treatment period. The main adverse effects are wheeze, cough, night awakening, and discoloured sputum, with most adverse events occurring in the first day after bronchoscopy and resolving within one week. In the AIR2 study, more hospital admissions occurred in the BT group (8.4%) compared with subjects in the sham group (2%) during the treatment phase.[28] Over the entire study period (from the day of the first bronchoscopy to the 12-month follow-up) there was no difference in the number of respiratory-related hospital admissions per subject in BT group (0.13, 10.5% of subjects) compared with the sham group (0.14, 5.1% of subjects).[15]

The results of these extension studies show the respiratory adverse events, lung function, and rates of hospital admissions or emergency department are unchanged in years 2 to 5 following the AIR[16], RISA[17], and AIR2 trials[18] (Table 2). Of the AIR2 subjects treated with BT who were followed up to 5 years, 97 patients (57%) underwent serial CT scans, which revealed no clinically significant structural abnormalities to the airways, except for three subjects who had increased or new bronchiectasis compared with the baseline.[18] In the BT10+ studies, 6 of the 89 participants (7%) treated with BT who did not have bronchiectasis at baseline developed bronchiectasis after treatment. All but one instance of bronchiectasis was classified as mild; one case was classified as moderate. Clinical symptoms of bronchiectasis were not present in these participants.[19]

(2) BT: Clinical efficacy and safety in real life case series and registry

The introduction of BT to clinical practice involves the treatment of real-life patients with moderate and severe asthma, some of them do not meet the inclusion and exclusion criteria used in the clinical trials. These results will give data on patient characteristics, efficacy and safety of BT in daily clinical practice.

The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma Study, the PAS2 study, is a U.S. FDA-mandated prospective observational "real-life" study designed to resemble the AIR2 trial in its patient population and outcome. This is a prospective, open-label, multicentre observational post-market study mandated by the FDA. This study included the first 190 subjects from the FDA-mandated PAS2 real-life registry. The objective is to compare outcomes in BT subjects (over three years of follow-up) from the ongoing, post-market PAS2 study with those from the AIR2 trial.[20] In this study,

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36%
Reduction in annualized rate of
moderate or severe exacerbations[1]
Rate ratio (95% CI), 0.64
(0.52, 0.78); p<0.001

42%
Reduction in annualized rate of
severe exacerbations[1]
Rate ratio (95% CI), 0.58
(0.45, 0.73); p<0.001

ENERZAIR® BREEZHALER® :IND/GLY/MF 150/50/160µg (once-daily); SAL/FLU high-dose = SAL/FLU 50/500µg (twice-daily)
*In symptomatic asthma patients, despite treatment with medium- or high-dose LABA/ICS.[1]
**Secondary analysis, not controlled for multiplicity – analyzed using a generalized linear model assuming the negative binomial distribution.[1] 52-week randomized study in 3,092 asthma patients, inadequately controlled on medium- or high-dose ICS/LABA.[1]

ENERZAIR® BREEZHALER® Important note: Before prescribing, consult full prescribing information. **Presentation:** Inhalation powder hard capsules containing indacaterol (as acetate) 150 micrograms, glycopyrronium 50 micrograms and mometasone furoate 160 micrograms respectively. **Indications:** Enerzair Breezhaler is indicated as a maintenance treatment of asthma in adult patients not adequately controlled with a maintenance combination of a long acting beta2 agonist and a high dose of an inhaled corticosteroid who experienced one or more asthma exacerbations in the previous year. **Dosage and administration: Adults:** The recommended dose is one capsule to be inhaled once daily. ♦The maximum recommended dose is Enerzair Breezhaler 150/50/160 micrograms once daily. **Pediatric patients (below 18 years):** The safety and efficacy of Enerzair Breezhaler in paediatric patients below 18 years of age have not been established. No data are available. **Special populations:** ***Renal impairment:*** No dose adjustment is required in patients with mild to moderate renal impairment. Caution should be observed in patients with severe renal impairment or end stage renal disease requiring dialysis. ***Hepatic impairment:*** No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available for the use of the medicinal product in patients with severe hepatic impairment, therefore it should be used in these patients only if the expected benefit outweighs the potential risk. ***Geriatric patients:*** No dose adjustment is required in elderly patients (65 years of age or older) **Method of administration:** ♦For inhalation only. Must not be swallowed. Patients who do not experience improvement in breathing should be asked if they are swallowing the capsule rather than inhaling it. ♦The capsules must be administered only using the inhaler provided with each new prescription. ♦Should be administered at the same time of the day each day; can be administered irrespective the time of the day. ♦After inhalation, patients should rinse their mouth with water without swallowing. ♦If a dose is missed, it should be taken as soon as possible. Patients should be instructed to not take more than one dose in a day. ♦Enerzair Breezhaler capsules must always be stored in the blister to protect from moisture and light, and only removed immediately before use. **Contraindications:** ♦Hypersensitivity to any of the active substances or excipients. **Warnings and precautions:** ♦**Deterioration of disease:** Should not be used to treat acute asthma including acute episodes of bronchospasm. A short acting bronchodilator should be used. Patients should not stop treatment without physician supervision since symptoms may recur after discontinuation. It is recommended that treatment with this medicinal product should not be stopped abruptly. ♦**Hypersensitivity:** If hypersensitivity reaction occurs, Enerzair 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, Enerzair Breezhaler should be discontinued immediately and alternative therapy instituted. ♦**Cardiovascular effects:** Like other medicinal products containing beta2-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. Should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension, known or suspected prolongation of the QT interval), convulsive disorders, thyrotoxicosis, or in patients who are unusually responsive to beta2-adrenergic agonists. ♦**Hypokalemia:** Beta2-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe condition, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias. ♦**Hyperglycemia:** Inhalation of high doses of beta2-adrenergic agonists and corticosteroids may produce increases in plasma glucose. Upon initiation of treatment with Enerzair Breezhaler, plasma glucose should be monitored more closely in diabetic patients. ♦**Anticholinergic effects:** Use with caution in patients with narrow-angle glaucoma and urinary retention. Patients should be advised about signs and symptoms of acute narrow angle glaucoma and should be instructed to stop treatment and to contact their doctor immediately should any of these signs or symptoms develop. ♦**Patients with severe renal impairment:** Caution should be observed in patients with severe renal impairment or end stage renal disease requiring dialysis. ♦**Prevention of oropharyngeal infections:** In order to reduce the risk of oropharyngeal candida infection, patients should be advised to rinse their mouth or gargle with water without swallowing it or brush their teeth after inhaling the prescribed dose. ♦**Systemic effects of corticosteroids:** Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods. Should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. ♦**Excipients:** This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. **Pregnancy:** Should only be used if the expected benefit to the patient justifies the potential risk to the fetus. **Lactation:** A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. **Labor and delivery:** Like other medicinal products containing beta2-adrenergic agonists, indacaterol may inhibit labor due to a relaxant effect on uterine smooth muscle. **Adverse drug reactions:** ♦**Very Common (≥10%):** nasopharyngitis, asthma (exacerbation) ♦**Common (≥1% to <10%):** upper respiratory tract infection, candidiasis, urinary tract infection, hypersensitivity, headache, tachycardia, oropharyngeal pain, cough, dysphonia, gastroenteritis, musculoskeletal pain, muscle spasms, pyrexia. ♦**Uncommon (≥0.1% to <1%):** hyperglycaemia, cataract, dry mouth, rash, pruritus, dysuria. **Interactions:** ♦**Beta2-adrenergic blockers:** Should not be given together with beta2-adrenergic blockers (including eye drops) unless there are compelling reasons for their use. ♦**Medicinal products prolong QTc interval:** Should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval ♦**Hypokalemic treatment:** Concomitant treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalemic effect of beta2-adrenergic agonists. ♦**CYP3A4 and P-glycoprotein inhibitors:** Inhibition of CYP3A4 and P-gp has no impact on the safety of therapeutic doses of Enerzair Breezhaler. ♦ **Other long acting antimuscarinics and long acting beta2-adrenergic agonists:** Co-administration with other medicinal products containing long-acting muscarinic antagonists or long-acting beta2adrenergic agonists is not recommended. ♦**Cimetidine or other inhibitors of the organic cation transport:** No clinically relevant drug interaction is expected. **Packs:** 30 x 1 hard capsules, together with 1 inhaler. **Legal classification:** P1S1S3 Last revision: Sep 2021 Ref: EU May 2021

Reference: 1. Kersjens H, *et al. Lancet Respir Med* 2020;8(10):1000-1012.

The materials for Enerzair contained in this virtual exhibition are approved for use only in Hong Kong. Prescribing information may vary depending on local approval in each country / location. Therefore, before prescribing any product, always refer to local materials such as the prescribing information and/or the Summary of Product Characteristics (SPC)

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Table 1: Bronchial thermoplasty randomised controlled trails (Excerpted from Cox G, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007;356: 1327-37.[13], Pavord ID, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med 2007;176: 1185-91.[14], Castro M, Rubin AS, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: A multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010;181: 116-24.[15])

Trial (design) [Ref.], year	Patients, *n*	Follow-up, months	Pre-FEV1 Baseline, % pred. (BT vs. control)	Primary endpoint (BT vs. control)	Main (secondary) endpoints (BT vs. control)
AIR (RCT) [13], 2007	112	12	72.7 vs. 76.1	Improvement in mild exacerbation rate (per patient/week) -0.16 vs. 0.04 (p = 0.005)	Improvement in AQLQ, ACQ, morning peak expiratory flow, asthma symptom-free days, and symptom scores
RISA (RCT) [14], 2007	32	12	62.9 vs. 66.4	Safety: short-term increase in asthma-related morbidity; long-term improvement	Improvement in AQLQ, ACQ, and pre-FEV1 Reduction in rescue medication use
AIR2 (RCT, sham controlled) [15], 2010	288	12	77.8 vs. 79.7	Improvement in AQLQ (1.35 vs. 1.16) (PPS 0.96)	Reduction in severe exacerbations, emergency department visits, and days missed from work/school

BT, bronchial thermoplasty; RCT, randomised controlled trail; FEV1 % pred., forced expiratory volume in 1 s percent predicted; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; PPS, posterior probability of superiority.

Table 2: BT 5-year long-term follow-up studies and real-world registration (Excerpted from Thomson NC, Rubin AS, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma intervention research (AIR) trial. BMC Pulm Med 2011;11:8.[16], Pavord ID, Thomson NC, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol 2013;111: 402-7.[17], Wechsler ME, Laviolette M, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013;132: 1295-302.[18], Chupp G, Laviolette M, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: A comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J 2017;50:1700017.[20])

Trail (design) [Ref.]	Patients (BT treated), *n*	Follow-up, years	Main outcomes
AIR (extension study) [16]	45	5	Stable FEV1 and long-term safety profile
RISA (extension study)[17]	14	5	Stable FEV1, reduction in hospitalisations and emergency department visits
AIR2 (extension study)[18]	162	5	Stable FEV1 and long-term safety profile including chest HRCT 44% decrease in exacerbations 78% decrease in emergency department visits
PAS 2 (post-FDA-approval study)[20]	190	3	Stable FEV1 45% decrease in severe exacerbations 55% decrease in emergency department visits 40% decrease in hospitalisations

BT, bronchial thermoplasty; FEV1, forced expiratory volume in 1 s; HRCT, high-resolution computed tomography.

patients recruited had more severe asthma as a baseline characteristic of having more exacerbations (74% vs 52%) and hospitalisations (15.3% vs 4.2%) in the 12 months prior to BT than the AIR2 study patients. They were older in age and carried more comorbidity and higher BMI. There was also a higher proportion of subjects taking maintenance oral corticosteroids (18.9% vs 4.2%). The study showed that at three years' post-treatment, there was a significant reduction of 45% in severe exacerbation, 55% in emergency department visits, and 40% in hospitalisation rate respectively in patient treated with BT (Table 2).[20] This real life study finding echoes the finding of the previous AIR2 study in terms of efficacy and safety; this real life study has extended the positive findings to patients having more severe asthma, more comorbidities associated with higher BMI and older age.

Other than the PAS2 study, there are several large cohorts of the patients under the national registry that had been treated with BT and had reported positive results in clinical outcome parameters with favourable safety profiles.

The first UK real life series was published in 2015 and showed that clinical improvements occurred in 50% of the clinic patients.[22] In 2017, Burn J et al. reported the result of the British Thoracic Society (BTS) Difficult Asthma Registry and Hospital Episodes Statistics database of 59 patients with severe refractory asthma undergoing BT from 2011 to 2015. Patients in these groups on the average were older, had worse baseline FEV1 and lower AQLQ scores compared with published RCT trials.[23] This is a safety study and the results showed that a higher proportion of patients experienced adverse events compared with clinical trials. The

greater severity of disease amongst patients treated in clinical practice may explain the observed rate of post-procedural stay and readmission.

The results of the United Kingdom Severe Asthma Registry of 86 patients undergoing bronchial thermoplasty were published in 2019, namely clinically significant improvements in AQLQ at 12 months of follow-up and reductions in hospital admissions at 24 months. However, improvements were not seen in all patients and an exploration of the characteristics of 'responders' to BT could only identify age as a possible predictor of outcome.[24]

The Australian group had first published their result in 2017 on 20 patients who received BT from 2014 to 2015.[25] Patient treated had more severe asthma at baseline with lower FEV1 (range: 33-95%) and more patients (50% of patients) on oral corticosteroid. Seventeen patients (85%) achieved a clinically significant improvement in asthma-related quality of life. Daily reliever salbutamol usage, and exacerbations requiring systemic corticosteroids were also significantly reduced in the study cohort. Five of the 10 patients who are on long-term oral corticosteroids had completely discontinued maintenance oral corticosteroids.

In 2020, the data of the Australian BT registry was published and the first 77 patients consecutively enrolled for treatment were included for analysis.[26] BT resulted in a significant improvement in the ACQ score. The exacerbation frequency and SABA requirement were reduced significantly, and 48.8% of the patients were weaned completely off oral steroids. A significant improvement in FEV1 was observed. Using multiple linear regression modelling, baseline ACQ score strongly predicted improvement in ACQ score ($P < 0.001$). Patients with an exacerbation frequency greater than twice in the previous 6 months showed the greatest reduction in exacerbations ($P < 0.001$). Patients using more than 10 puffs/d of SABA experienced the greatest reduction in SABA requirement (-12.4 ± 10.5 puffs, $P <0.001$). The authors concluded that the most severely afflicted patients had the greatest improvements in ACQ score, exacerbation frequency, and medication requirement.[26]

Using the same patient cohort, the Australian group published another article to address the safety and effectiveness of BT when FEV1 is less than 50%.[27] In the analysis, patients were grouped according to baseline FEV1 < 50% or >= 50% predicted. The result showed that efficacy and safety outcomes were the same between these two lung function groups. Eighty-seven percent of patients reached a minimally clinical important difference improvement in scores on the ACQ Asthma Control Questionnaire, and 50% of the patients were able to discontinue systemic steroids at six months. A comparison of the two lung function groups demonstrated that BT is safe attaining the same efficacy in patients with severe airflow obstruction.

There is another recently published global registry study that gives further support to the efficacy of BT in treating severe asthma. The global Bronchial Thermoplasty Global Registry (BTGR) is a prospective, open-labelled, single-arm, observational registry designed to collect outcome data as well as clinical and demographic characteristics of patients undergoing BT treatment in the 'real-world' clinical setting. BTGR-enrolled subjects from 23 January 2014 to 28 December 2016 at 18 centres in Spain, Italy, Germany, the UK, the Netherlands, the Czech Republic, South Africa and Australia. Between 2014 and 2016, the BTGR enrolled 157 subjects aged 18 years and older who were scheduled to undergo BT treatment. In 2 years after BT treatment, reductions in several asthma maintenance medications were observed when compared with baseline. Mean daily ICS dose had been reduced from 1721±1239 μg/day to 1217±912 μg/day ($p=0.013$), and, importantly, the proportion of subjects using maintenance oral corticosteroids (OCS) was significantly reduced from 47.8% to 24.8% by two years after BT ($p=0.0002$). The proportion of subjects using biologics was also reduced from 9.6% at baseline to 5.7% at two years after BT ($p=0.045$).[28] The results of the BTGR concurred with the results from previously published studies and indicate that in the BTGR population, subjects undergoing treatment with BT achieved reductions in severe asthma exacerbations and other healthcare utilisation as well as reductions in asthma maintenance medication usage, particularly oral corticosteroids.

In summary, patients treated with bronchial thermoplasty in real life clinical practice have more severe disease than those recruited to AIR and AIR2 trials. All these real life registry data across the world provide consistent data that BT is safe and effective in severe asthma patients, even in patients with severe airflow obstruction.

The 2022 GINA Guideline has outlined the treatment algorithm for severe asthma.[1,2] The GINA recommendation for BT in severe asthma is as follows: GINA recommends considering BT as one add-on treatment in patients with no evidence of type 2 airway inflammation as well as in patients with type 2 airway inflammation but with no good response to type 2-targeted therapy (Evidence B).[2]

CONCLUSION

Severe asthma represents a heterogeneous patient group. Patients with non-T2 asthma comprise a group of poorly defined asthma patients. Therapies for non-T2 asthma are limited when compared with T2 asthma.) Currently biologics for non-T2 asthma is disappointing. Azithromycin has been found to be useful in recent studies and has been included as an add-on option in international asthma guidelines. Studies have shown safety of use when precautions are taken before starting treatment. Bronchial thermoplasty is a non-pharmacological bronchoscopic treatment that should be considered. Existing trials on bronchial thermoplasty have demonstrated a clear effectiveness signal and an excellent long-term safety and effectiveness record, with published data beyond 10 years. Real world data further supports findings of the original randomised control trials. The latest GINA guideline has well defined a position for macrolides and bronchial thermoplasty respectively in the treatment algorithm in managing non-T2 asthma patients or in T2 asthma patients who do not respond to biologics.

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Objectives:

To provide an updated understanding in hot topics of allergy.

Date	Topics	Speakers
21 July 2022	Allergen specific immunotherapy: the clinical applications	Dr. Alson W. M. CHAN Specialist in Paediatric Immunology Allergy & Infectious Diseases
28 July 2022	Allergy, diet & nutrition	Ms. Sabrina W. S. MOK Registered Dietitian
4 Aug 2022	Oral immunotherapy for food allergy	Dr. Gilbert T. CHUA Clinical Assistant Professor Department of Paediatrics & Adolescent Medicine The University of Hong Kong
11 Aug 2022	Urticaria: new treatment updates	Dr. Marco H. K. HO Specialist in Paediatric Immunology Allergy & Infectious Diseases
18 Aug 2022	Anaphylaxis: the new developments	Dr. Agnes S. Y. LEUNG Assistant Professor Department of Paediatrics The Chinese University of Hong Kong
25 Aug 2022	Updates in allergy diagnostics	Dr Adrian Y. Y. WU Specialist in Allergy & Immunology

Date : 21, 28 July & 4, 11, 18, 25 August 2022 (Every Thursday)
Duration of session: 1.5 hours (6 sessions)
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CME / CNE / CDE (Dietitians) Accreditation in application
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Asthma and Pregnancy

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INTRODUCTION

The prevalence of asthma in Hong Kong is approximately 5%, affecting women more often than men. As such, asthma in pregnancy may be encountered by doctors across various specialties. Poorly controlled asthma and asthma exacerbations can impose risks to maternal and foetal health, and would create a complex challenge. The prevalence of asthma in pregnancy varies in studies ranging from 3.6% to 12.4%,[1,2] but there are not yet local data on the prevalence of asthma in pregnancy in Hong Kong.

POOR CONTROL AND EXACERBATION MAY AFFECT MATERNAL AND FOETAL HEALTH

A Swedish population-based study of more than 260,000 pregnant ladies showed that maternal asthma was associated with a number of serious pregnancy complications and adverse perinatal outcomes, including preeclampsia or eclampsia, premature contractions, low birth weight, and small for gestational age.[3] On the contrary, Schatz, in his cohort of 486 asthmatic pregnant women, found no significant increase in the incidences of preeclampsia, perinatal mortality, pre-term births or low birth weight, when compared with control.[4] It is noteworthy that the asthmatic women in Schatz's study were well managed with stepwise therapy to minimise asthma symptoms and prevent acute asthmatic exacerbations. It is postulated, based on studies showing an association between poorly-controlled asthma and asthma exacerbations with adverse outcomes, that the adverse outcomes are caused by chronic hypoxia. Namazy found in a meta-analysis that asthma exacerbations, oral corticosteroid use and asthma severity were associated with pre-term delivery, low birth weight and small for gestational age infants.[5] Murphy in another meta-analysis also noted that pregnant women with a severe exacerbation were at increased risk of delivering a low-birth-weight baby.[6] Abdullah, in his 10,3424 pregnant women cohort, found that asthma exacerbations during pregnancy were associated with an increased risk of pregnancy complications (pre-eclampsia and pregnancy-related hypertension), adverse perinatal outcomes (pre-term delivery, low birth weight and congenital abnormalities) and early childhood respiratory disorders (asthma and pneumonia) in their children.[7] Optimising the management of asthma in pregnancy to avoid exacerbations is therefore of paramount importance.

RISK FACTORS FOR ASTHMA EXACERBATION IN PREGNANCY

The course of asthma in pregnancy varies. It is classically taught that approximately one-third of patients improve, one-third experience worsening symptoms and the remaining one-third remain unchanged during pregnancy. This has been derived from a review of nine retrospective studies showing that 36% of patients improved, 23% worsened and 41% remained similar during pregnancy.[8] There is no evidence that type 2 airway inflammation increases during pregnancy. However, pregnancy-related hormonal changes, gastro-oesophageal reflux and microaspiration, and increased susceptibility to viral infections may contribute to exacerbations.[9]

Asthma exacerbations during pregnancy occur primarily in the late second trimester.[10] Baibergenova found that the emergency department visits peaked in the second trimester and declined afterwards, and asthma exacerbations were rare in labour.[11] Furthermore, patients with severe asthma prior to pregnancy carry a higher risk of asthma exacerbations during pregnancy. Bakern, in his meta-analysis of 1,461 patients, found that a history of asthma exacerbations and poor asthma control despite treatment with moderate-to high-dose inhaled corticosteroids or long-acting beta-agonists predicted severe asthma exacerbations during pregnancy.[12] Other risk factors for asthma exacerbations during pregnancy include inadequate prenatal care, obesity and lack of appropriate treatment with inhaled corticosteroids. Stenius, in his cohort of 504 asthmatic pregnant women, found that only 3.9% of patients on inhaled corticosteroids had an asthma exacerbation during pregnancy, compared with 17.5% of patients not on inhaled corticosteroids.[13] Poor drug adherence could be a barrier, as up to 17-30% of pregnant women reported that they would reduce or stop asthma medication during pregnancy.[14,15] Patients should be advised to maintain good asthma control, and medication adherence should be reinforced. Viral infections are another well-known trigger of asthma exacerbations in the general population, and it holds true in pregnancy as viral infections as a trigger were reported in 34% of pregnant women in one study.[16] Pregnant women are more susceptible to viral infections as a result of decreased cell immunity; both the Centers for Disease Control and Prevention (CDC) in the United States, and the Centre for Health Protection (CHP) in Hong Kong have recommended to provide influenza vaccination to pregnant women. Given the current

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The course aims to develop a better understanding of prostate cancer, which includes screening guidelines, symptoms, staging and diagnosis. The course will provide information about treatments and therapies for localized and advanced prostate cancer. The course will also introduce innovations technology that can improve patient safety and enhance treatment efficiency for prostate cancer.

Date	Topics	Speakers
20 July 2022	Prostate cancer: From screening to establish diagnosis - new tools	Dr. FUNG Tat Chow, Berry Specialist in Urology
27 July 2022	Imaging of prostate cancer	Dr. CHAN Tin Sang, Augustine Specialist in Radiology
3 August 2022	Treatment of organ-confined prostate cancer	Dr. CHENG Kwun Chung, Bryan Specialist in Urology
10 August 2022	The role of radiotherapy in prostate cancer	Dr. YEUNG Sin Yu, Cynthia Specialist in Clinical Oncology
17 August 2022	Noval therapy for metastatic castration-resistant prostate cancer (mCRPC)	Dr. LEUNG Kwong Chuen, Angus Specialist in Clinical Oncology
24 August 2022	Prostate cancer: Innovations to improve patient safety and enhance treatment efficiency	Dr. MAK Siu King Specialist in Urology Mr. KU Ki Man, Imen Chief Radiation Therapist

Date : 20, 27 July & 3, 10, 17, 24 August 2022 (Wednesday)
Duration of session: 1.5 hours (6 sessions)
Time : 7:00 pm - 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Quiz for doctors: DOCTORS are required to complete a quiz after the completion of each lecture
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$1,000
Certificate : Awarded to participants with a minimum attendance of 70% (4 out of 6 sessions)
Deadline : 14 July 2022
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

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COVID-19 pandemic at the time of this writing, the CDC, CHP and the Hong Kong College of Obstetricians and Gynaecologists have recommended COVID vaccination to pregnant women.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

The diagnosis of asthma is usually already known prior to pregnancy. However, in a patient without a previous diagnosis of asthma, asthma should be differentiated from other respiratory illnesses. The Global Initiative for Asthma (GINA)[17] suggests the diagnosis to be made by both the characteristic pattern of respiratory symptoms and the evidence of variable airflow limitation. Symptoms including wheezing, chest tightness, cough, and shortness of breath classically vary with time or change with a diurnal variation. Triggers like cold weather, allergens, exercise and laughter may sometimes be identified. Spirometry with post-bronchodilator reversibility test can be performed to document airflow limitation and reversibility; positive reversibility is commonly defined as an increase by 12% and more than 200 ml in the forced expiratory volume in 1 second (FEV1). However, bronchial challenge tests including methacholine, mannitol or hypertonic saline test are not recommended.[18] Although effort should be made to identify allergens in atopic asthma, a skin prick test should be postponed after delivery due to a small risk of anaphylaxis. In vitro tests, i.e. allergen-specific Immunoglobulin E are however recommended during pregnancy. Dyspnea of pregnancy, in which wheezing or airway obstruction is usually not present, is a common differential diagnosis which may affect up to 70% of pregnant women.

MONITORING AND FOLLOW-UP

The GINA guidelines recommend providing asthmatic patients with a written asthma action plan.[17] A study showed education on asthma self-management with a written action plan led to improved asthma symptoms and reduced use of reliever medications in pregnant subjects.[19] Fraction of exhaled Nitirc Oxide (FE_{NO}) has been a hot topic in recent years for the management of asthma. FE_{NO} could act as a surrogate marker of type 2 airway inflammation in asthma. Powell, in his randomised controlled trial (RCT) of 220 pregnant women with asthma, found that treatment adjustment according to FE_{NO} level could reduce exacerbation rates by half.[20] Interestingly, in the follow up study of Powell's RCT, the offsprings in the FE_{NO}-guided treatment were found to have a lower prevalence of childhood asthma when compared to the control arm.[21] The same medical team performed a larger RCT of 1,200 pregnant women with asthma, but this larger study could not demonstrate any statistically significant difference in terms of adverse perinatal outcomes between FE_{NO}-driven treatment and usual care.[22]

Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT) are good tools to assess asthma control in patients. Araujo[23] found in asthmatic pregnant women, there was a high correlation between asthma control test scores and clinical control of asthma as defined by the GINA. The GINA[17] suggests a stepwise approach in the management of asthmatic patients such that medications are titrated according to asthma control. Although the GINA recommends follow-up at 1-3 months after starting treatment and at every 3-12 months thereafter for general asthmatic patients, a closer and regular follow-up of every one month is recommended by the National Asthma Education and Prevention Programme in the United States for asthmatic pregnant women.[24]

NON-PHARMACEUTICAL AND PHARMACEUTICAL TREATMENT

Pregnant asthmatic smokers should be advised to quit smoking and efforts should be made to identify and avoid allergens in all patients. Adherence to anti-inflammatory therapies should be reinforced. A study showed that in pregnant patients not initially treated with inhaled corticosteroids, 17% had an acute attack. In those who had been on inhaled corticosteroids from the start of the pregnancy, this number drops to 4%.[13] International guidelines recommend treating pregnant asthmatic women similarly as non-pregnant patients.[17,24,25] A large population-based case-control study found common asthma medications would be safe in pregnant women.[26] Use of inhaled corticosteroid, inhaled beta-2-agonists, cromolytes, theophylline and montelukast is not associated with an increased incidence of foetal abnormalities.[15,27] Measurement of theophylline level is recommended as decrease in protein binding during pregnancy may lead to increased drug level.[25] Although oral corticosteroid use has been reported to be associated with perinatal adverse effects, many experts believe the adverse effects to be reflective of the disease severity and exacerbations instead. This is supported by studies showing a risk reduction after controlling maternal disease activity. It is generally believed that the advantages of actively treating asthma outweigh any potential risks of the usual medications. Among the injectable biologics for asthma, no increased risk of foetal anomalies was associated with omalizumab. At the time of writing, there have not yet been registries of pregnant human subjects using other biologics.[28]

PERIPARTUM MANAGEMENT

Although asthma exacerbation is rare during labour, perhaps due to endogenous corticosteroid production, pregnant women should be advised to continue their usual asthma medication while in labour. Patients receiving oral steroids exceeding prednisolone 7.5 mg daily should receive "stress cover" steroids, i.e. parenteral hydrocortisone 100 mg every 6-8 hours. If anaesthesia is required, epidural anaesthesia is preferred as it reduces oxygen consumption and minute ventilation, and provides adequate analgesia.[25] Magnesium and terbutaline[29] can be used as tocolytic agents for the management for acute pre-term labour, while indomethacin should be avoided given the possible risk of bronchospasm, especially in aspirin-sensitive asthma. Oxytoxcin is the preferred drug for labour induction and postpartum haemorrhage. While prostaglandin E1 (PGE1) misoprostol and PGE2 (dinoprostone) are deemed safe for labour induction, PGF2α (dinoprost) should be avoided for postpartum

haemorrhage as it may cause bronchoconstriction. Breastfeeding is encouraged, as usual medications to treat asthma have been shown to be safe in lactating women.[25]

CONCLUSION

Although asthma complicating pregnancy may be a clinical challenge, current evidence suggests usual medications are safe in pregnancy and it is of paramount importance to control asthma well to minimise risks to maternal and foetal health.

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Mechanical Ventilation in Acute Severe Asthma

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INTRODUCTION

Globally among all chronic respiratory diseases, asthma is ranked the second leading cause of death.[1] Approximately 2% to 20% of Intensive Care Unit (ICU) admissions are attributed to acute severe asthma, and up to one third of these ICU admissions require intubation and invasive mechanical ventilation (IMV).[2] Of a total of 38,325 patients who were hospitalised for asthma in Hong Kong from January 2015 to April 2020, 426 patients (1.11%) required mechanical ventilation, and 133 patients (0.34%) died.[3] Mortality increased to 10% to 20% among the intubated, mostly as a consequence of cardiopulmonary arrest before ICU admission.[4]

In this paper, we would like to review (1) the role of non-invasive ventilation (NIV), (2) points to note when intubating a patient with acute severe asthma, and (3) ventilation strategies to minimise dynamic hyperinflation and its adverse consequences.

ACUTE SEVERE ASTHMA

An asthma exacerbation is characterised by the progressive increase in symptoms of cough, wheezing and/or chest tightness from the patient's baseline condition necessitating a change in treatment.[5] Acute severe asthma or exacerbation, also known as status asthmaticus, is an exacerbation unresponsive to standard treatment and can result in hypoxaemia, hypercapnoeia, and respiratory failure. It is a medical emergency that may warrant treatment with mechanical ventilation.

ROLE OF NON-INVASIVE VENTILATION IN ASTHMA

Theoretically, NIV offers the advantages of overcoming intrinsic positive end-expiratory pressure (PEEPi) from gas trapping and of reducing inspiratory and expiratory work of breathing (WOB). However, NIV can lead to gastric distension and dyssynchrony especially if the patient is agitated and claustrophobic.

To date, it remains uncertain whether the theoretical benefits of NIV can be translated into clinical outcome benefits as existing randomised controlled trials have been underpowered.[6-7] Large retrospective cohort studies in the United States have demonstrated that NIV use was associated with decreased odds of IMV and mortality, but these studies also cautioned the use of NIV in those with acute comorbid conditions such as pneumonia, severe sepsis and acute renal failure, as these conditions are associated with a higher NIV failure rate, and a higher in-patient mortality rate if they fail NIV compared to the overall study population.[8,9] The 2017 European Respiratory Society and American Thoracic Society (ERS/ATS) clinical practice guidelines are unable to offer a recommendation for NIV in acute respiratory failure due to asthma based on the current evidence.[10]

In settings where the patient can be closely monitored and rapid intervention is feasible, it is reasonable to carry out an NIV trial. Criteria for patient selection are those needing ventilatory assistance, in the absence of contraindications (Table 1).[11]

Table 1. Indications and contraindications for non-invasive ventilation (Adapted from Noninvasive positive pressure ventilation in acute asthmatic attack. European Respiratory Review 2010; 19:39-45)

Indications	Contraindications
• Moderate-to-severe respiratory distress (use of accessory muscles, paradoxical breathing)	• Need for immediate intubation as in respiratory or cardiac arrest
• Respiratory rate > 25 breaths per minute	• Unable to protect the airway
• Heart rate > 110 beats per minute	• Recent upper airway or oesophageal surgery
• Heart rate > 110	• *Haemodynamic instability
• PaO2/FiO2 ratio < 200 mmHg	• *Excessive secretions
• PaCO2 > 45 mmHg	• *Poor patient cooperation, severe agitation
	• *Unable to fit mask

** Relative contraindications*
FiO2, Fraction of inspired oxygen; PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen

Patients must be closely monitored and reassessed at 1 to 2 hours after initiating NIV. In the absence of an improvement in arterial partial pressure of carbon dioxide (PaCO2), pH, oxygenation, and/or respiratory rate (RR), the patient should be promptly intubated to avoid delaying IMV and increasing mortality. The HACOR scale, which considers the heart rate, presence of acidosis, conscious level, adequacy of oxygenation, and RR, is a useful bedside tool for the prediction of NIV failure.[12]

INTUBATION TECHNIQUE

Indications for intubation and mechanical ventilation are near or total respiratory or cardiac arrest, altered sensorium, progressive exhaustion, silent chest, severe hypoxaemia (PaO2 < 60 mmHg) with maximal oxygen delivery, and failure to reverse severe respiratory acidosis (pH < 7.2, PaCO2 > 55 to 70 mmHg) despite intensive therapy.[13]

Orotracheal intubation is generally preferred as it allows insertion of a larger-sized endotracheal tube to facilitate secretion clearance and carbon dioxide (CO2) removal. Asthmatic patients are more likely to have nasal polyps and sinus pathology, which may complicate nasotracheal intubation.[14] Sedation and muscle paralysis, and pretreatment with bronchodilators make intubation smoother and prevent eliciting bronchospasm and laryngospasm.

Induction with ketamine (1 to 1.5 mg/kg) or propofol (2 mg/kg) is preferred for their bronchodilatory effects.[15] The downside of ketamine is hypersecretion and catecholamine release, the latter contraindicating the use of ketamine in patients with ischaemic heart disease, hypertension, pre-eclampsia and increased intracranial pressure. Opioids such as morphine are routinely avoided; although the clinical significance of histamine release is doubtful,[14] other side effects of opioids such as hypotension, nausea and vomiting preclude its routine use at intubation.

Succinylcholine as a paralytic agent offers rapid onset and short duration of action but causes a greater histamine release, which could theoretically worsen bronchospasm,[16] although the clinical significance is again doubtful. However, succinylcholine can increase potassium level. This may aggravate pre-existing hyperkalemia associated with respiratory acidosis, and may potentially lead to life-threatening cardiac arrhythmia. As for non-depolarising agents such as rocuronium, since they carry a longer duration of action, it is important to assess for a difficult airway before inducing muscle paralysis.

IMMEDIATE POST-INTUBATION MANAGEMENT

In the early phase of the disease, within 24 to 48 hours of intubation, deep sedation is often necessary to reduce oxygen consumption and CO2 production, promote patient-ventilator synchrony, and enforce controlled hypoventilation. Propofol or benzodiazepines together with a narcotic such as fentanyl to suppress respiratory drive are recommended to reduce high dose propofol use, which may rarely lead to propofol infusion syndrome and seizure.

Neuromuscular blockade may at times be necessary. Intermittent bolus is preferred over continuous infusion to allow respiratory muscles to rest while lessening the risk of myopathy.[17]

AIM OF MECHANICAL VENTILATION

The aim of mechanical ventilation is to achieve adequate ventilation, improve oxygenation, and relieve respiratory distress, while avoiding the complications of mechanical ventilation. In acute severe asthma and other obstructive airway diseases, the markedly increased airway resistance predisposes to the development of dynamic hyperinflation and its complications.

ASSESSMENT OF DYNAMIC HYPERINFLATION

Dynamic hyperinflation occurs when there is incomplete exhalation of each tidal volume (Vt) because of diminished expiratory flow. The alveoli have not emptied to their resting functional residual capacity (FRC) by the end of exhalation. Clinically, expiratory flow fails to reach zero at the initiation of the next breath (Fig. 1A). This results in breath stacking and progressively increased lung volume. Increased lung volume raises elastic recoil pressure and distends the airways, increasing expiratory flow until eventually, the delivered tidal volume can again be completely exhaled. A new equilibrium is then established, but with tidal breathing taking place at a raised lung volume.

The raised lung volume and intrathoracic pressure of dynamic hyperinflation lead to the following adverse consequences: (1) Barotrauma and ventilator-induced lung injury (VILI), (2) Hypotension because of reduced venous return, decreased left ventricular compliance and increased right ventricle afterload from raised pulmonary vascular resistance, (3) Increased WOB as inspiration takes place in the upper and less compliant part of the pressure-volume curve near total lung capacity, and (4) Increased triggering threshold compromising patient-ventilator synchrony resulting in ineffective and/or delayed triggering.

Volume above FRC at end-inspiration (Vei) is the reference technique to quantify dynamic hyperinflation. Vei greater than 20 ml/kg is a reliable predictor of complications.[18,19] The original technique involves passive exhalation from end-inspiration into a burette or volumetric spirometer and is cumbersome. In clinical practice, PEEPi and plateau airway pressure (Pplat) are measured as surrogates of dynamic hyperinflation (Fig. 1).

The residual positive pressure within the lungs at end-expiration referenced to atmospheric pressure or to PEEP applied through a ventilator (the extrinsic PEEP; PEEPe) is referred to as intrinsic or auto-PEEP (PEEPi).[17] This can be measured by a brief expiratory pause (Fig. 1C), when the patient is passive (sedated or paralysed) to factor out expiratory muscle activity leading to falsely high PEEPi. However, PEEPi underestimates dynamic hyperinflation in the presence of airway closure, thus preventing accurate measurement of alveolar pressure. Pplat is considered a better estimation of dynamic hyperinflation in non-obese patients.[20] Pplat reflects the elastic recoil pressure at end-inspiration and is

measured by a brief inspiratory pause (Fig. 1A & 1B). A Pplat > 30 cmH2O indicates excessive hyperinflation and risks of complications.[19]

Peak airway pressure (Ppeak) is highly dependent on inspiratory flow-resistive properties and inspiratory time. It does not reflect the degree of hyperinflation and risk of barotrauma.

Capnogram analysis is useful in demonstrating bronchospasm as a cause of dynamic hyperinflation. Varying degrees of bronchospasm causes the alveoli to have heterogeneous ventilation/perfusion ratio and varying alveolar pCO2. Alveolar units exhale at different time points resulting in turbulent mixing of dead space air with alveolar air and softening the normally rapid rise in CO2 concentration. A 'shark fin' or sawtooth waveform is observed. Return of normal rectangular waveform indicates resolution of bronchoconstriction.

Fig. 1: Ventilator tracings in airway obstruction. All four figures are ventilator screenshots from a Servo-U ventilator in volume-control mode connected to a lung simulator configured with raised resistance. (Clinical photos from personal collection)

Fig. 1A: Flow-time scalar (green tracing) showed that expiratory flow had not reached zero at the start of the next inspiration (red arrows), resulting in breath stacking and dynamic hyperinflation.

Fig. 1B: Pplat (yellow circle) can also be measured by activating inspiratory hold. Pplat measured at the end of inspiration of the pressure-time scalar (yellow tracing) was 32 cmH2O, exceeding the recommended value of below 28-30 cmH2O.

Fig. 1C: Total PEEP (white circle) can be measured by activating expiratory hold. PEEPi can be calculated from total PEEP minus set PEEPe (11 - 6 = 5 cmH2O).

Fig. 1D: A more appropriate ventilator setting with controlled hypoventilation: a small Vt of 6-8 ml/ kg predicted body weight and a lower RR. Note that expiratory flow has reached zero at the start of each inspiration. Pplat was kept below 28-30 cmH2O. RR could be further adjusted to blood gas result.

VENTILATION STRATEGIES

Volume-limited modes like assist control ventilation (ACV) or synchronised intermittent mandatory ventilation (SIMV) are sometimes to pressure-limited modes,[18] because firstly, constant flow shortens the inspiratory time and lengthens expiratory time. Secondly, Ppeak and Pplat can be directly monitored (Fig. 1), and thirdly, in case bronchospasm breaks, an exceedingly high Vt can be avoided. However, constant flow only prolongs expiration to a minor degree and its effect on dynamic hyperinflation is minimal. There is no clinical advantage of using one mode over another as long as minute ventilation, the major determinant of hyperinflation, is controlled.

Controlled hypoventilation is recommended for acute severe asthma to reduce dynamic hyperinflation. The initial ventilator setting includes a small Vt of 6-8ml/ kg ideal body weight, a high inspiratory flow rate (60 - 90 L/min) to preserve expiratory time, a slow RR at 10 to 15 breaths per minute, and ensuring expiratory flow returns to zero before the initiation of the next breath.[19] PEEPi should be minimised to below 10

cmH2O and Pplat kept below 28 - 30 cmH2O (Fig. 1D).[20,21] If Pplat exceeds 30 cmH2O, minute ventilation (RR and Vt) should be reduced, and other causes of a raised Pplat such as pneumothorax should be excluded. Pharmacological treatment for acute severe asthma should be optimised at the same time.

Controlled hypoventilation to minimise dynamic hyperinflation and its adverse consequences takes precedence over normalising blood gases and PaCO2 (permissive hypercapnia). Although hypercapnoeia can raise intracranial pressure and cause pulmonary hypertension, pH > 7.2 and PaCO2 < 80 mmHg are often well tolerated. Additionally, hypercapnoeia can be improved by changing a heat-and-moisture exchanger (HME) to a heated humidifier and removing other apparatus dead space such as a catheter mount.

The responses to PEEPe in patients with airway obstruction were described previously.[18] As the response is variable and unpredictable, it is worthwhile to interrogate Pplat response in passive patients. Raising PEEPe is useful only if it leads to a paradoxical decrease in hyperinflation and Pplat.[22] On the other hand, PEEPe should not be increased if it results in a concomitant rise in Pplat, which signifies worsening of dynamic hyperinflation because of reduced expiratory pressure gradient and flow. In spontaneously breathing patients, PEEPe of up to 80% of PEEPi can overcome ineffective or delayed triggering secondary to dynamic hyperinflation.[23] Neurally-adjusted ventilatory assist (NAVA), through utilising patient's electrical activity of the diaphragm (Edi) to triggering inspiration, cycling expiration, and adjusting pressure delivery accordingly to breathing effort, could minimise patient-ventilator dyssynchrony irrespective of PEEPi.[24] It may be useful in difficult-to-wean patients. It is, however, only available in the Servo ventilators and requires a dedicated Edi catheter.

CONCLUSION

Acute severe asthma is a potentially life-threatening medical emergency. Early recognition and prompt treatment can be lifesaving. Those who require mechanical ventilation face significant morbidity and mortality. It is essential to apply mechanical ventilation appropriately in these patients to avoid ventilator-induced lung injury that would otherwise worsen outcome.

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Exploring American's Wild West

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Dr Wendy WS TSUI

The wilderness of the American West has always attracted the attention of travellers, for exploration and for adventure. My husband and I had the opportunity to visit four of these scenic National Parks: Bryce Canyon, Antelope Canyon, Monument Valley and Arches National Park in 2019. Our trip started in Salt Lake City, the capital city of the State of Utah and a well-known religious centre of the Mormons.

The first National Park we visited was Bryce Canyon. Here, we could find the iconic geological feature called hoodoos (tall, thin and irregularly eroded spires of rocks) standing inside the Amphitheatre. Bryce Canyon holds the largest collection of hoodoos in the world. To explore the Amphitheatre in detail, we hiked the Sunset Point Navajo Loop Trail, which is a 2.4 km trail taking us from the Amphitheatre rim to the floor and back. There are 13 stop points along the trail where visitors can stop to enjoy the spectacular views of various clusters of hoodoos.

(Personal collection)

From Bryce Canyon, we drove 430 km south to the city of Page, Arizona. We visited the spectacular Horseshoe Bend, where the Colorado River makes a hair-pin turn to create this magnificent landscape and stunning topography. Standing on the cliff 300 metres above the Colorado River is breathtaking and one really feel being on the top of the world.

(Personal collection)

On the following day, we visited the Upper and Lower Antelope Canyon, a world-famous and unique geological landscape called Slot Canyon. Slot Canyon describes the narrow, slit-like gorges created by the erosion of rushing water into soft rocks such as sandstone and limestone over millions of years. Antelope Canyon is one of the busiest tourist attractions and walking in the Canyon is comparable to shopping in Causeway Bay on a Sunday. The landscape and scenery are truly stunning and breathtaking. It is a paradise for photographers and a dreamland for ordinary visitors.

(Personal collection)

Leaving the beautiful Antelope Canyon, we drove 200 km east to arrive at the Monument Valley Navajo Tribal Park. You can see the famous West Mitten Butte, East Mitten Butte and Merrick Butte, which are synonymous with America's mythic "Wild West". These gigantic sandstone pillars (called buttes) rise 100-300 metres above the valley floor and are created by the erosion of wind and water over the Colorado Plateau. You can drive through the 27 km unpaved Valley Drive to see the spectacular views of these geological wonders inside Monument Valley.

(Personal collection)

Finally, we turned 238 km north from the Monument Valley and arrived at the city of Moab to pay our visit to the Arches National Park. There are more than 2,000 sandstone arches inside the park and some of the world-famous arches such as the Landscape Arch, Double

Arch, Delicate Arch and Balance Rock can be easily accessible by car. Sunset is particularly beautiful as one can see these sandstone arches turning red by the glow of the receding sun. It is truly breathtaking to see these magnificent craftwork of mother nature.

(Personal collection)

Special Article

The Hong Kong College of Dermatologists (formerly known as Hong Kong Association of Specialists in Dermatology) was established in 2005. The College was established with the intention to safeguard public interest to ensure patients in need of specialist care are able to receive optimal management from clinicians engaged in the practice of dermatology. Dermatologists treat more than 1,000 conditions that affect the skin, hair and nails, ranging from common conditions like warts, acne, eczema, psoriasis and cosmetic concerns to potential life-threatening malignant melanoma and Stevens-Johnson syndrome. Skin diseases are especially common affecting one in ten people in Hong Kong each year.

The prime objective of the College is to promote the highest standard of dermatological patient care and skin health of people in Hong Kong through the advancement of dermatology which includes the investigation, preservation and restoration of the form and function of the skin, and associated structures by medical, surgical, and physical means with the aim of bringing relief to patients of all ages suffering from the effects of injury or disease of the skin. The Hong Kong Society for Paediatric Dermatology has been affiliated with the College to advance education and care of skin disease in paediatric age groups since 2010.

Our mission is to promote the optimal skincare and standard of care for dermatological patients through professional scientific educational activities to clinicians and allied disciplines through our Annular Scientific Meeting and various seminars. Taking into account the demand for accurate and reliable information on common skin conditions by members of the public, we promote better education and health care awareness of the public in dermatological diseases and dermatology as a specialty through media events and our website.

In order to promote and encourage medical training, research and education on dermatology and related therapy through certificate courses, monographs and articles. The College also collaborates with The Hong Kong Society of Dermatology & Venereology to publish The Hong Kong Journal of Dermatology & Venereology (HKJDV) which is indexed in EMBASE/Excerpta Medica, Science Citation Index Expanded (SCIE) and Scopus. The College is the largest and most representative dermatologist group in Hong Kong and aims to represent the dermatological profession in the above objectives in negotiations and interactions with other associations and similar bodies locally and internationally.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	★Zoom Live HKMA Conference on Telemedicine - Online 1) Introduction to the MCHK's Ethical Guidelines on Practice of Telemedicine 2) Practical tips about the new guidelines on telemedicine 3) A Global Guide to Telehealth Policies 4) Case Studies on Telemedicine practice 4
5	6	★Zoom Live HKMA-HKSH CME Programme 2021-2022 (Online) Topic: Updates of Neuroimmunology ★Professorial Webinar From Translational Research to Clinical management - Hereditary Breast Cancer 7	★The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed 8	★Zoom Live Personalized Angina Management in Patients with Novel Medication and Cardiac Shock Wave Therapy - Online 9	★Zoom Live Management of Adrenal Incidentaloma - Online 10	11
12	★Zoom Live Dual Pathway Inhibition in Coronary Artery Disease - Online 13	14	15	★Zoom Live HKMA-HKSTP CME Lecture - Rhinitis , Sinusitis and Nasopharyngeal carcinoma (Online) 16	★Zoom Live Personalized Management of Nonsmall Cell Lung Cancer - Online 17	18
19	20	★Zoom Live HKMA-GHK CME Programme 2021 - 2022 - Strategies of Tumor Clearance in Management of Colorectal Diseases (Online) 21	★Zoom Live Latest Updates on COVID-19 Vaccines in Children and Adolescents - Online 22	★Zoom Live Why Early and Tight Glycemic Control Remain Essential for T2DM Patient? - Online 23	★Zoom Live Varicose Vein and Treatment Option - Online ★15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong) 24	★15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong) 25
★15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong) 26	27	28	★Zoom Live Recent Updates On The Management Of Rheumatoid Arthritis - Online 29	30		

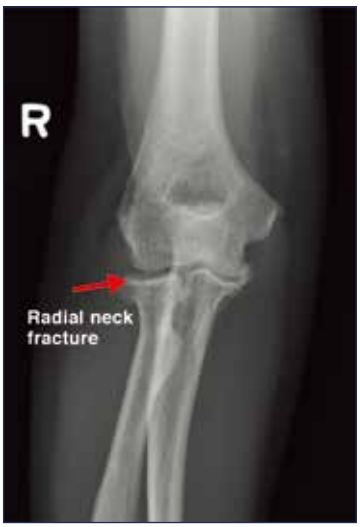
Date / Time	Function	Enquiry / Remarks
4 SAT 2:30 PM	**Zoom Live** **HKMA Conference on Telemedicine - Online** **1) Introduction to the MCHK's Ethical Guidelines on Practice of Telemedicine** **2) Practical tips about the new guidelines on telemedicine** **3) A Global Guide to Telehealth Policies** **4) Case Studies on Telemedicine practice** Organiser: Hong Kong Medical Association Speaker: Dr YEUNG Hip-wo, Victor, Mr Woody CHANG, Ms Christine TSANG and Mr David KAN	HKMA CME Dept. 3108 2507 3 CME Points
7 TUE 2:00 PM	**Zoom Live** **HKMA-HKSH CME Programme 2021-2022 (Online)** **Topic: Updates of Neuroimmunology** Organiser: Hong Kong Medical Association & Hong Kong Sanatorium & Hospital Speaker: Dr SHIU Ka-lock	HKMA CME Dept. 3108 2507 1 CME Point
7:30 PM	**Professorial Webinar** **From Translational Research to Clinical management – Hereditary Breast Cancer** Organiser: Hong Kong Chinese Medical Association Ltd. Speaker: Professor Ava KWONG	HKCMA Ms Stone Tse 2527 8898 1CME Point
8 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting –To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker: Dr CHEUNG Wing Lok	Dr Calvin MAK 2595 6456 1.5 CME Point
9 THU 2:00 PM	**Zoom Live** **Personalized Angina Management in Patients with Novel Medication and Cardiac Shock Wave Therapy - Online** Organiser: HKMA-KLN East Community Network Speaker: Dr GOH King-man, Victor	Mr Jeffrey CHEUNG 3108 2514 1 CME Point
10 FRI 2:00 PM	**Zoom Live** **Management of Adrenal Incidentaloma - Online** Organiser: HKMA-YTM Community Network Speaker: Dr KAN Mei-yee, Daisy	Ms Candice TONG 3108 2513 1CME Point
13 MON 2:00 PM	**Zoom Live** **Dual Pathway Inhibition in Coronary Artery Disease - Online** Organiser: Hong Kong Medical Association Speaker: Dr LO Ka-yip, David	HKMA CME Dept. 3108 2507 1CME Point
16 THU 2:00 PM	**Zoom Live** **HKMA-HKSTP CME Lecture - Rhinitis , Sinusitis and Nasopharyngeal carcinoma (Online)** Organiser: Hong Kong Medical Association & Hong Kong Science Park Speaker: Dr LAM Chuen-kwong	HKMA CME Dept 3108 2507 1CME Point
17 FRI 2:00 PM	**Zoom Live** **Personalized Management of Nonsmall Cell Lung Cancer - Online** Organiser: HKMA-KLN City Community Network Speaker: Dr AU Siu-kie	Ms Candice TONG 3108 2513 1CME Point
21 TUE 2:00 PM	**Zoom Live** **HKMA-GHK CME Programme 2021 - 2022 - Strategies of Tumor Clearance in Management of Colorectal Diseases (Online)** Organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital Speaker: Dr LEUNG Lik-hang, Alex	HKMA CME Dept 3108 2507 1CME Point
22 WED 2:00 PM	**Zoom Live** **Latest Updates on COVID-19 Vaccines in Children and Adolescents - Online** Organiser: Hong Kong Medical Association Speaker: Dr SHAM Chak-on, Philip	HKMA CME Dept. 3108 2507 1CME Point
23 THU 2:00 PM	**Zoom Live** **Why Early and Tight Glycemic Control Remain Essential for T2DM Patient? - Online** Organiser: HKMA-HK East Community Network Speaker: Dr. WONG Cheuk-lik	Ms Candice TONG 3108 2513 1CME Point
24 FRI 2:00 PM	**Zoom Live** **Varicose Vein and Treatment Option - Online** Organiser: HKMA-Shatin Community Network Speaker: Dr. CHIU Nga-king	Ms Candice TONG 3108 2513 1CME Point
(25,26)	**15th Congress of Asian Society of Cardio-vascular Imaging (ASCI 2022 Hong Kong)** Venue: Hong Kong Convention & Exhibition Centre Organisers: Hong Kong College of Radiologists & Hong Kong College of Cardiology Format: Hybrid (In-person & Online)	ASCI 2022 Congress Secretariat Tel: (852) 2559 9973 Email: info@asci-2022.org Website: https://www.asci-2022.org
29 WED 2:00 PM	**Zoom Live** **Recent Updates On The Management Of Rheumatoid Arthritis - Online** Organiser: Hong Kong Medical Association Speaker: Dr. WONG Ching-han, Priscilla	HKMA CME Dept. 3108 2507 1CME Point

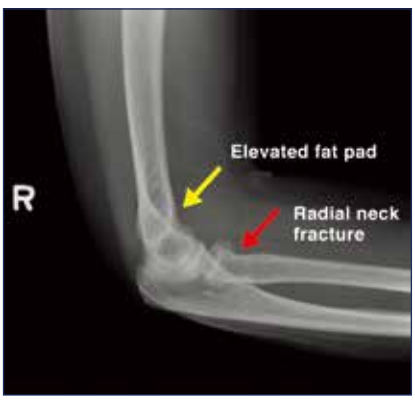
Answers to Radiology Quiz

Answers:

1. Cortical break noted over the right radial neck, suspicious for a nondisplaced fracture. There is an elevation of the anterior fat pad on lateral view, suggestive of a joint effusion. The radiocapitellar and anterior humeral lines are preserved.

2. Radial neck fractures are usually not displaced. As a result, they are usually treated with immobilisation in cast. In the rare situation where there is a transverse fracture of the neck and displacement of the proximal fracture fragment, operative intervention may be required.





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Avamys
fluticasone furoate
鼻眼適

gsk

風繼續吹，塞左個鼻

每日1次[1]

英國製造

鼻眼適 連續10年銷售No.1[3,4]

有效舒緩鼻敏感症狀[1]

無藥味、無倒流[2]

大人小朋友都用得[*1]

*兩歲或以上適用

請向醫護人員查詢有關詳情。商標為葛蘭素史克集團擁有或經授權使用。

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Reference: 1. Avamys Hong Kong Prescribing Information Version GDS11v4/TGA20181204 .2. Berger WE, Godfrey JW, Slater AL. Intranasal corticosteroids: the development of a drug delivery device for fluticasone furoate as a potential step toward improved compliance. Expert Opin. Drug Deliv 2007 4(6): 689-701. 3. IQVIA Sales Data (GP Channel) in class R01A1 (NASAL CORTIC W/O ANTIHNF), 2015-2020. 4. HKAPI Sales Data (Private) in class R1A (Topical Nasal Preparations), 2009-2014

Safety Information: AVAMYS is contraindicated in patients with a history of hypersensitivity to any components of the preparations. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroids are prescribed concurrently. Infection of the nasal airways should be appropriately treated but does not constitute a contraindication to treatment with AVAMYS. Nasopharyngeal candidiasis can occur in patients treated with intranasal steroids, as a class effect. The lowest dose of AVAMYS that causes suppression of the HPA axis, effects on bone mineral density or growth retardation has not yet been established. However, the systemic bioavailability of fluticasone furoate is low (estimated at 0.50%) when given as AVAMYS and this limits the potential for systemic side effects. As with other intranasal corticosteroids, physicians should be alert for evidence of systemic effects including ocular changes. Growth retardation has been reported in children receiving some nasal corticosteroids at licensed doses. It is recommended that the height of children receiving prolonged treatment with nasal corticosteroids is regularly monitored. No clinical studies have been conducted to investigate interactions of fluticasone furoate on other drugs. Based on data with another glucocorticoid metabolised by CYP3A4, co-administration with ritonavir is not recommended because of the potential risk of increased systemic exposure to fluticasone furoate. Adverse Reactions: Very common; epistaxis and nasopharyngitis, Common; nasal ulcerations and headache. Please refer to the full prescribing information for further details.

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PM-HK-FLI-FSTR-210004 (1/2/2023) Date of preparation: 02/01/2022

The **FIRST AND ONLY** asthma biologic to inhibit IL-4 and IL-13 signaling

AN ADD-ON MAINTENANCE TREATMENT FOR PATIENTS (12+ YEARS) WITH **INADEQUATELY CONTROLLED SEVERE ASTHMA** WITH TYPE 2 INFLAMMATION[1]

A CLEAR PATH TO ASTHMA CONTROL

NOW AVAILABLE

UP TO 72% REDUCTION

SIGNIFICANT EXACERBATION REDUCTION

in annualized severe exacerbations at Week 24 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*=0.0003)[1]

86% OF PATIENTS

REDUCED OR NO INCREASE IN THEIR OCS DOSE

by Week 24 with DUPIXENT 300 mg Q2W + SOC vs 68% with placebo + SOC (P<0.001)[2]

200 mL IMPROVEMENT

RAPID AND SUSTAINED IMPROVEMENT IN LUNG FUNCTION

at Week 52 with DUPIXENT 200 mg Q2W + SOC vs placebo + SOC (*P*<0.001)[3]

UP TO 75% OF PATIENTS

HIGH RESPONDER RATE

in Asthma Control Questionnaire measures of **sleep, activity limitations, and breathing**[1]

SELF-INJECTABLE

Convenient subcutaneous injection[1]

LIBERTY ASTHMA VENTURE Study Design[2]: 210 patients were randomly assigned with oral glucocorticoid-treated asthma to receive add-on DUPIXENT (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV_1) before bronchodilator use were also assessed.

LIBERTY ASTHMA QUEST Study Design[1]: 1902 patients who were 12 years of age or older with uncontrolled asthma were randomly assigned in a 2:2:1:1 ratio to receive add-on subcutaneous DUPIXENT at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimetre. Asthma control and DUPIXENT safety were also assessed.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid ; OCS, oral corticosteroid; Q2W, once every 2 weeks; SOC, standard of care.

References: 1. DUPIXENT Summary of Product Characteristics. May 2020. **2.** Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med. 2018;378(26):2475-2485. **3.** Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018;378(26):2486-2496.

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. **Indications:** Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week. AD adolescents: Body weight <60 kg- initial dose of 400 mg (two 200mg injections), followed by 200 mg every other week. Body weight ≥60 kg- same dosage as adults. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma: Initial dose of 400 mg, followed by 200 mg every other week. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD- initial dose of 600 mg, followed by 300 mg every other week. Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. If a dose is missed, administer it asap and thereafter, resume dosing at the regular scheduled time. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Safety and efficacy in children <12 years not been established. Not to be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Patients who develop conjunctivitis that does not resolve following standard treatment should undergo ophthalmological examination. AD patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Do not give live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** AD: Most common adverse reactions reported- injection site reactions, conjunctivitis, blepharitis and oral herpes. Safety profile observed in adolescents consistent with that seen in adults. Asthma: Most common adverse reaction reported- injection site erythema. For other undesirable effects, please refer to the full prescribing information. Preparation: 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.** API-HK-DUP-20.05

MAT-HK-2000267-1.0-08/2020 4IC.1408

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