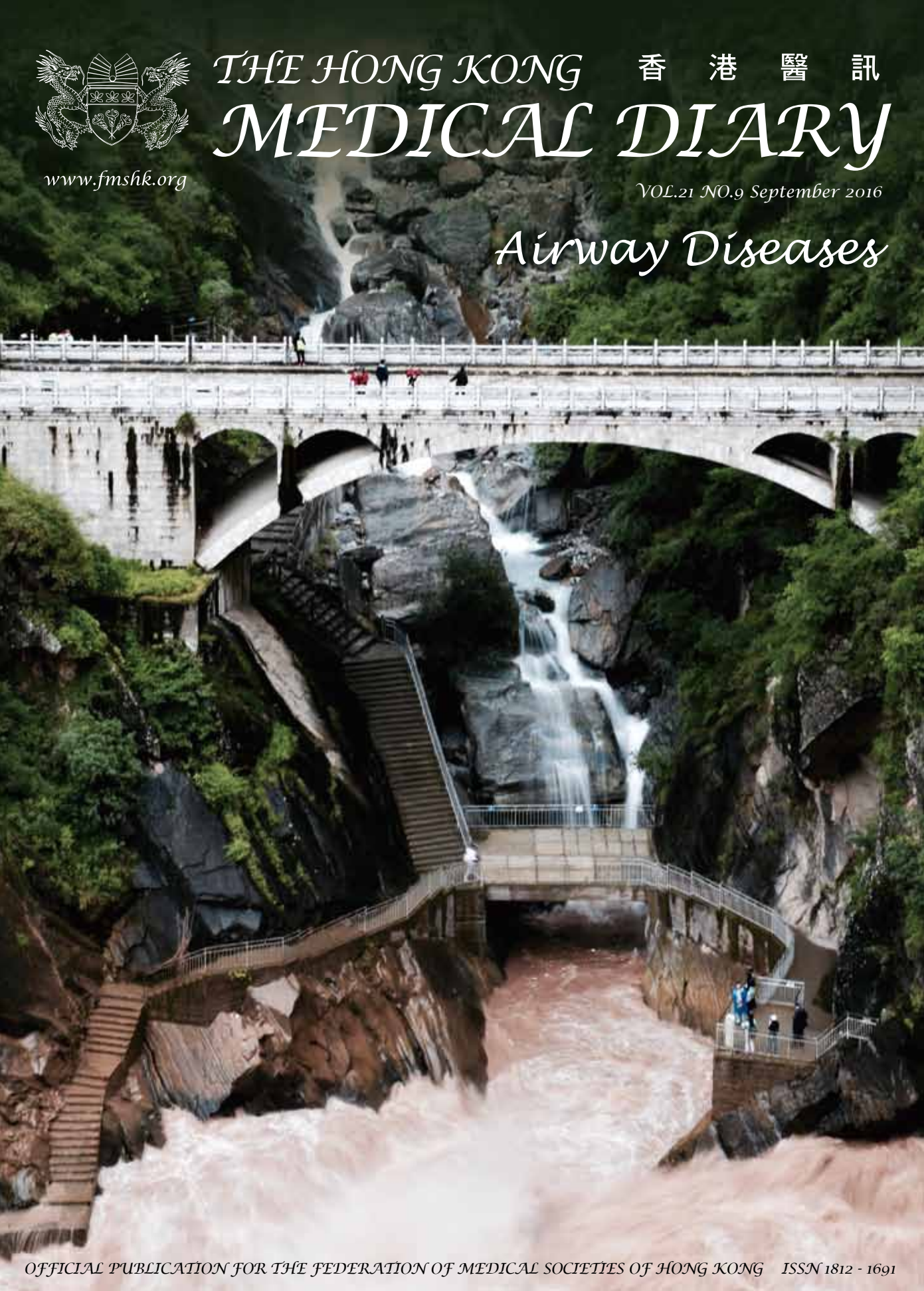
www.fmshk.org

THE HONG KONG MEDICAL DIARY

香港醫訊

VOL.21 NO.9 September 2016

Airway Diseases



OFFICIAL PUBLICATION FOR THE FEDERATION OF MEDICAL SOCIETIES OF HONG KONG ISSN 1812 - 1691

ULTIBRO® BREEZHALER®

POWERFUL EFFICACY TO START A NEW CHAPTER IN COPD[1-3]

Vs Tiotropium[2]

SIGNIFICANT REDUCTION OF

14%

ALL EXACERBATIONS

Vs Fluticasone / Salmeterol[3]

SIGNIFICANT DECREASE OF

31%

MODERATE OR SEVERE EXACERBATIONS

ULTIBRO® BREEZHALER®

Important note: Before prescribing, consult full prescribing information. **Presentation:** Inhalation powder hard capsules containing indacaterol maleate equivalent to 110 microgram (mcg) indacaterol and glycopyrronium bromide equivalent to 50 microgram glycopyrronium. **Indications:** ULTIBRO® BREEZHALER® is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). **Dosage: Adults:** recommended dosage is the once-daily inhalation of the content of one 110/50 mcg capsule using the ULTIBRO BREEZHALER inhaler. **Children (<18 years):** should not be used in patients under 18 years of age. **Special patients population:** *Renal impairment:* can be used at recommended dose in patients with mild to moderate renal impairment. Should be used only if expected benefit outweighs the potential risk in patients with severe renal impairment or end-stage renal disease requiring dialysis. *Hepatic impairment:* Can be used at the recommended dose in patients with mild and moderate hepatic impairment. No data are available for subjects with severe hepatic impairment. *Geriatrics:* can be used at recommended dose in patients 75 years of age and older. **Method of administration:** ULTIBRO BREEZHALER capsules must be administered by the oral inhalation route and only using the ULTIBRO BREEZHALER inhaler. Capsules must not be swallowed. ULTIBRO BREEZHALER should be administered at the same time of the day each day. If a dose is missed, it should be taken as soon as possible. Patients should be instructed not to take more than one dose in a day. Capsules must always be stored in the blister to protect from moisture, and only removed immediately before use. Patients should be instructed on how to administer the product correctly. Patients who do not experience improvement in breathing should be asked if they are swallowing the medicine rather than inhaling it. **Contraindications:** ◆known hypersensitivity to indacaterol, which is one of the components of ULTIBRO BREEZHALER, or to any of the excipients. **Warnings/Precautions:** ◆ULTIBRO BREEZHALER should not be administered concomitantly with other long-acting beta-agonists or long-acting muscarinic-antagonists. ◆**asthma:** should not be used in asthma. Novartis Page 2 BSS ULTIBRO BREEZHALER long-acting beta-adrenergic agonists may increase the risk of asthma-related serious adverse events, including asthma-related deaths, when used for treatment of asthma ◆**not for acute use:** should not be used as rescue therapy ◆**hypersensitivity related to indacaterol:** If hypersensitivity reaction occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆**paradoxical bronchospasm:** as with other inhalation therapy, administration may result in paradoxical bronchospasm that may be lifethreatening. If paradoxical bronchospasm occurs, ULTIBRO BREEZHALER should be discontinued immediately and alternative therapy instituted ◆**anticholinergic effects related to glycopyrronium:** use with caution in patients with narrow-angle glaucoma and urinary retention ◆**systemic effects of beta-agonists:** as with other beta-adrenergic agonists, should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension); in patients with convulsive disorders or thyrotoxicosis; in patients who are unusually responsive to beta-adrenergic agonists ◆**patients with severe renal impairment:** to be used only if expected benefit outweighs potential risk in patients with severe renal impairment including end-stage renal disease requiring dialysis. ◆**cardiovascular effects of beta-agonists:** like other beta- adrenergic agonists, may produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, blood pressure, and/or symptoms, ECG changes ◆**hypokalemia with beta-agonists:** beta-adrenergic agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. In patients with severe COPD, hypokalemia may be potentiated by hypoxia and concomitant treatment which may increase the susceptibility to cardiac arrhythmias ◆**hyperglycemia with beta agonists:** clinically notable changes in blood glucose (4.1%) at the recommended dose than on placebo (2.3%), ULTIBRO BREEZHALER has not been investigated in patients for whom diabetes mellitus is not well controlled. **Women of child-bearing potential:** There are no special recommendations for women of child-bearing potential. **Pregnancy:** should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus. **Breast-feeding:** should only be considered if the expected benefit to the woman is greater than any possible risk to the infant. **Fertility:** reproduction studies or other data in animals did not reveal a problem or potential problem concerning fertility in either males or females. **Labor and delivery:** *Information related to indacaterol* - ULTIBRO BREEZHALER may inhibit labor due to a relaxant effect on uterine smooth muscle. **Interactions:** ◆No specific drug-drug interaction studies were conducted with ULTIBRO BREEZHALER. Information on the potential for interactions is based on the potential for each of its two components. ◆should not be given together with beta-adrenergic blockers (including eye drops) unless there are compelling reasons for their use ◆should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT-interval. Drugs known to prolong the QT-interval may Novartis Page 3 BSS ULTIBRO BREEZHALER increase the risk of ventricular arrhythmia. ◆concomitant administration of other sympathomimetic agents may potentiate the undesirable effects ◆concomitant treatment with methylxanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate the possible hypokalemic effect of beta2-adrenergic agonists. ◆inhibition of the key contributors of indacaterol clearance, CYP3A4 and P-gp, has no impact on safety of therapeutic doses. ◆co-administration with other inhaled anticholinergic-containing drugs has not been studied and is therefore not recommended. ◆no clinically relevant drug interaction is expected when glycopyrronium is co-administered with cimetidine or other inhibitors of the organic cation transport. **Adverse reactions:** *Adverse reactions from ULTIBRO BREEZHALER* ◆**Uncommon (≥0.1 to <1%) and potentially serious:** Glaucoma, hypersensitivity, diabetes mellitus and hyperglycemia, ischemic heart disease, atrial fibrillation, paradoxical bronchospasm ◆**Very common (≥10%):** Upper respiratory tract infection ◆**Common (≥1% to <10%):** Nasopharyngitis, urinary tract infection, sinusitis, rhinitis, dizziness, headache, cough, oropharyngeal pain including throat irritation, dyspepsia, dental caries, gastroenteritis, musculoskeletal pain, pyrexia, chest pain ◆**Uncommon (≥0.1% to <1%):** Insomnia, paresthesia, tachycardia, palpitations, epistaxis, dry mouth, pruritus/rash, muscle spasm, myalgia, pain in extremity, bladder obstruction including urinary retention, peripheral edema, fatigue, **Packs and prices:** 30 Inhalation Powder Hard Capsules/Pack **Legal classification:** P1S1S3 Ref: EMA Oct 2013

References:

1. ULTIBRO BREEZHALER Local Prescription Information 2014.
2. Wedzicha JA et al. Lancet Resp Med. 2013 ;1:199–209.
3. Nanshan Zhong et al. Int. Journal of COPD. 2015 ;10:1015–1026.

ONCE DAILY ultibro® breezhaler®

indacaterol maleate/glycopyrronium bromide inhalation powder

NOVARTIS **Novartis Pharmaceuticals (HK) Ltd** 27/F, 1063 King's Road, Quarry Bay, Hong Kong Tel: 2882 5222 Fax: 2159 7242

HK1601426081 Jan 2016

Contents

Disclaimer

The Cover Shot

Photo by Dr Jane Chan & family during trip to Yunnan in July 2016

Located in the Yunnan Province and as a major west-most tributary of the Yangtze River, the Tiger Leaping Gorge (虎跳峽) is one of the deepest river gorges in the world, spanning 2.5-3.0 Km from mountain peaks to the river surface and 17 Km in length. Its name originated from local legend that tigers could leap across the narrowest point of the river when preying.

Dr Jane CK CHAN

MD (Chicago), FHKCP, HKAM (Medicine)
Diplomate American Board of Internal Medicine
(Pulmonary Medicine & Critical care)
Specialist in Respiratory Medicine
In private practice

Published by
The Federation of Medical Societies of Hong Kong

Design and Production
A-PRO MULTIMEDIA LTD www.apro.com.hk

Editorial

Dr Chun-kong NG

MBBS (HK), MRCP (UK), HKCP, FHKAM (Med), MPH (HK), FRCP (Edin)

Consultant Respiratory Physician

Editor

Dr Chun-kong NG

Airway disease is one of the leading causes of morbidity and mortality in Hong Kong and throughout the world. The Burden of Lung Disease Study in 2005 showed that respiratory diseases, including airway diseases, was the leading cause of death, hospitalisation and health resources utilisation in Hong Kong. The World Health Organization estimated that COPD will become the 5th leading burden of disease and the 3rd leading cause of death by 2030.

In the past decades, we witnessed rapid advances in the management of airway diseases. Potent, once daily long acting bronchodilators, in single formulation or in combination forms improved the clinical efficiency in COPD management significantly. New biological therapies had been developed for the severe asthmatic patients who failed to respond to conventional treatments. New treatment options for bronchiectasis, like long term Macrolides, nebulised mucolytic and nebulised antibiotics improved patients' quality of life and reduced exacerbations. Non-pharmacological interventions were also introduced to the treatment armamentarium of airway diseases. Bronchial thermoplasty had been applied successfully in refractory asthmatic patients. Endobronchial valves were used to achieve medical volume reduction in selected COPD patients. Non-invasive home ventilation was offered to late-stage COPD patients having recurrent exacerbations and hospitalisations. In this issue of the Medical Diary, we will give you an up-to-date and comprehensive overview on these recent developments.

This issue on airway diseases is the collective work from some of the leading respiratory specialists in our local respiratory community. Dr Fanny KO is one of the leading expert in asthma management; Dr David LAM and Dr Macy LUI are renowned specialists in lung cancer and bronchiectasis management; Dr Johnny CHAN is one of the pioneers in the development of interventional pulmonology locally; Dr CM CHU and Dr Alice CHEUNG are leading pulmonologists in the application and research in non-invasive ventilation; and Dr Loletta SO and Dr Angus LO are experienced respiratory specialists in the management of chronic obstructive pulmonary disease.

We are also thankful to Dr Jane Chan for sharing her impressive photo taken at the 虎跳峽 in Yunnan and Dr YK LI for sharing his exciting stories and photos taken in Tanzania. These magnificent sceneries are truly the geological masterpieces created by Mother Nature.

I hope you will find these articles informative and helpful in your future management of patients with different airway diseases.

drug of choice
for allergic rhinitis[1,2]

Dymista® is the most recent addition to the allergic rhinitis (AR) medication toolbox. It comprises an INS (i.e. fluticasone propionate), an antihistamine (i.e. azelastine) and a novel formulation in a single spray. The result is a product which provides double the efficacy of INS and clinically relevant symptom control about a week faster.

References: 1. Carr W et al. A novel intranasal therapy of azelastine with fl uticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289. **2.** Leung DYM et al. MP29-02: A major advancement in the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1216.

MEDA

Interested in learning more about Dymista®?

- ❒ please send me further information on Dymista®.
- ❒ I would like to be visited by a MEDA representative.

Name: _____ Address: _____

Tel no.: _____ E-mail: _____

please send your request by fax: 2636 4619 or email: eddy.hui@medapharma.com

DYM-CSM-160726.1

Community **Atrial Fibrillation (AF)** Follow Up Program

Stroke is a leading cause of mortality and morbidity worldwide. **Atrial fibrillation (AF)** has increased the risk of stoke nearly 5-fold and its prevalence increases with age.[1]

AF-related strokes are highly preventable through early detection with follow up and appropriate treatment. However, AF is often diagnosed too late, normally at time of stroke, in approximately 20% of cases.[2]

Join Now!

2808 7807

@af.followup2016 @gmail.com

You are cordially invited to join the Community AF Follow Up Program through your participation and offering your professional consultation for potential AF patients.

Recruitment Target:

Doctors from private practices who have attended any certificate course about AF diagnosis and treatment*

Program Mechanism:

1. Invite patients from different Community AF Screening to participate.
2. Patients will register through program hotline and will be assigned to participating clinics randomly based on their preferred district.
3. AF disease education materials will be provided to participating doctors.
4. Participating doctors will diagnose patient with first consultation fee waived (medicine will be charged separately).

Please note that your participation in this study does not oblige you in any way to prescribe any products. We fully support your independent and professional judgment on the selection of treatment and/or medicine that best suits your patient's condition.

* Copy of the course certificate is required to be submitted and the panel from Hong Kong Practicing Specialists Networks (HKPSN) will evaluate if the course would be suitable. HKPSN reserves the final right to deny any registrations.

Ref:

1. Lloyd-Jones DM, Wang TJ, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–1046.
2. Simple awareness campaign in general practice identifies new cases of AF, European Society of Cardiology, Available at http://www.escardio.org/The-ESC/Press-Office/Press-releases/Last-5-years/Simple-awareness-campaign-in-general-practice-identifies-new-cases-of-AF, 2 Sep 2014.

香港執業專科醫生網絡
Hong Kong Practicing Specialists Network

Advances in Treatment of Severe Asthma

Dr Fanny Wai-san KO

Specialist in Respiratory Medicine
Department of Medicine and Therapeutics, The Chinese University of Hong Kong

Introduction

Asthma is a serious global health problem affecting all age groups. From the International Study of Asthma and Allergies in Childhood (ISAAC), it was observed that although there was little change in the overall prevalence of current wheeze across the globe, the percentage of children reported to have had asthma increased significantly.[1] In some countries, a decline in hospitalisations and deaths from asthma has been observed. However, asthma still imposes an unacceptable burden on health care systems, and on society through loss of productivity in the workplace, and especially for paediatric asthma, disruption to the family.[2] The prevalence of asthma ever and current wheeze were estimated to be 10.1 and 8.6% respectively among the 13-14 year old students in Hong Kong.[3] For elderly subjects in Hong Kong, the prevalence of physician diagnosed asthma among those aged ≥70 years was estimated to be 5.8% in 2003.[4]

The long-term goals of asthma management are to achieve good symptom control, and to minimise future risk of exacerbations, fixed airflow limitation and side-effects of treatment.[2] Guidelines like the Global Initiative for Asthma (GINA)[2] and British Thoracic Society guidelines[5] have suggested stepwise therapy for asthma with controller and reliever medications. Patients with milder disease would need less pharmacotherapy and more severe disease would need more medications and higher dosages for asthma control. Inhaled corticosteroid (ICS) and long acting beta agonist (LABA) are the mainstay controller treatment of asthma and majority of the asthma patients with good compliance and removal of triggering factor can have their asthma symptoms controlled with these medications. However, 5–10% of patients have limited treatment options and substantial morbidity due to the severity of their illness.[6]

In this article, we will discuss the advances in treatment of patients with severe asthma focusing on the use of biological therapy that has been approved by the Food and Drug Administration (FDA) of the United States for management of asthma. Bronchial thermoplasty is another therapy developed for the management of severe asthma and it is discussed in another article in the same issue of this Medical Diary.

Severe asthma

The European Respiratory Society and American Thoracic Society guidelines[6] define severe asthma as requiring management with high-dose ICS in addition to a second asthma controller, including the potential use of systemic corticosteroids. For a diagnosis of severe asthma to be made, this regimen has to be required to prevent symptoms from being uncontrolled or the symptoms are uncontrolled despite that treatment. Treatment for severe asthma is now focusing on tailoring to particular phenotypes driven by the endotypes.[6] Some biological therapies targeting the phenotype of eosinophilic asthma have been developed.

Biological therapy

Anti-immunoglobulin E therapy

Inappropriate immunoglobulin E (IgE)-mediated immune responses against normally tolerated environmental antigens represent a crucial pathogenetic process for the development of allergic diseases.[7] Omalizumab is a recombinant humanised monoclonal antibody developed by immunising mice with human IgE. It recognises IgE at the same site as the high-affinity receptor for IgE (Fc εRI) and forms complexes with free (unbound) IgE, blocking the binding of IgE to cell-membrane receptors, thereby inhibiting the release of mediators.[8] Omalizumab was approved by FDA in 2003 for adults and adolescents (≥12 years old) with moderate-to-severe persistent asthma who have a positive skin test result or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS. Patients should have total serum IgE concentration between 30 to 700 international units per mL (USA) or between 30 to 1500 international units per mL (European Union) and should not weigh more than 150 kg. It is administered subcutaneously to the patient every 2 to 4 weeks and has to be administered only under direct medical supervision (as anaphylaxis occurred in at least 0.1% of treated people) and the patient has to be observed for a minimum of 2 hours following administration of any dose given. Prescribers must be prepared and equipped to recognise and treat anaphylaxis should it occur.

A Cochrane database review[9] found that for subjects with moderate or severe asthma who were receiving background ICS therapy, there was a significant advantage favoured subcutaneous omalizumab with regard to experiencing an asthma exacerbation and reducing hospitalisations. Omalizumab was also significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. A randomised multicentre trial that included patients with inadequately controlled severe asthma who are receiving high-dose ICS and LABA showed a significant reduction in asthma exacerbations

(about 25%) and ability to decrease corticosteroid dose with omalizumab. Omalizumab improved asthma related quality of life, reduced mean daily albuterol and decreased mean asthma symptom score compared with placebo during the 48-week study period.[10] The difference in exacerbation frequency between omalizumab and placebo was greatest in subgroups with high levels of these three biomarkers: exhaled nitric oxide (FeNO), serum eosinophils and serum periostin.[11]

Treatment response of omalizumab should be globally assessed by the treating physician taking into consideration any improvement in asthma control, reduction in exacerbations and unscheduled health care utilisation, and improvement in quality of life. If a patient does not respond within 4 months of initiating treatment, it is unlikely that further administration of omalizumab will be beneficial.[6] Of patients with a good clinical response to omalizumab, about half relapse if it is discontinued, at a median of 13 months after discontinuation.[12]

Anti-interleukin 5

Interleukin (IL)-5 is a cytokine that is directly involved in the activation and recruitment of eosinophils.[13] Inhibiting IL-5 binding to eosinophils reduces blood, tissue, and sputum eosinophil levels. Mepolizumab, a humanised IgG1 kappa monoclonal antibody specific for IL-5, is an FDA-approved agent for treatment of asthma.[14] It is indicated for add-on maintenance treatment of patients with severe asthma aged 12 years or older and with an eosinophilic phenotype. The dosage is 100 mg administered subcutaneously every 4 weeks. Approval was based on three key phase 3 trials (DREAM[14], SIRIUS[15] and MENSA[16]).

In patients with uncontrolled eosinophilic asthma (blood eosinophils >150 cells per μL), in the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) study[14], Mepolizumab is an effective and well tolerated treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma. In the Steroid Reduction with Mepolizumab Study (SIRIUS), mepolizumab had a significant glucocorticoid-sparing effect, reduced exacerbations, and improved control of asthma symptoms among patients who required daily oral glucocorticoid therapy for maintaining asthma control. In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA)[16] study, it was found that in patients with eosinophilic asthma treated with high-dose ICS with or without maintenance oral glucocorticoids for asthma control, treatment with mepolizumab reduced exacerbations by approximately one half, improved quality of life, and resulted in better asthma control. Both intravenous and subcutaneous doses were effective and had acceptable side-effect profiles. The most frequently reported adverse events were nasopharyngitis and headache (each about 20%).

Reslizumab is an IgG4 kappa humanised monoclonal antibody that prevents binding of IL-5 to eosinophils. It has been approved by FDA in March 2016 and is indicated for add-on maintenance treatment of patients with severe asthma aged ≥18 years with an eosinophilic phenotype. It is administered as an intravenous infusion (3mg/kg) every 4 weeks.

In a randomised control trial involving patients with eosinophilic asthma (induced sputum eosinophils ≥3%) that was uncontrolled with high-dose ICS and at least one other agent, it was observed that patients receiving reslizumab showed significantly greater reductions in sputum eosinophils, improvements in airway function, and a trend toward greater asthma control than those receiving placebo. The improvements in asthma control were greater in patients with nasal polyposis.[17]

In another multicentre controlled trial that recruited asthma patients who were inadequately controlled by medium-to-high doses of ICS based therapy and who had blood eosinophils of 400 cells per μL or higher and one or more exacerbations in the previous year, it was found that patients who received reslizumab had a significant reduction in the frequency of asthma exacerbations compared with those receiving placebo.[18] The most common adverse events were worsening asthma symptoms, upper respiratory tract infections and nasopharyngitis.[18] Two out of the 477 patients in the reslizumab group in this trial had anaphylactic reactions and both responded to standard treatment at the study centre.[18]

Reslizumab should be considered in patients with uncontrolled eosinophilic asthma, especially patients with previous exacerbations, reduced lung function, or nasal polyposis.[13]

Other biological therapies

There are other biological agents that are potentially useful for treatment of patients with eosinophilic asthma. These agents have not yet received FDA approval. For example, benralizumab is an IgG1k monoclonal antibody that targets the human IL-5-receptor α expressed on basophils and eosinophils and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity.[13,19] Another example is Lebrikizumab is an IgG4 monoclonal antibody that targets IL-13.[20,21] Dupilumab that targets the α subunit of the IL-4 receptor can inhibit both IL-4 and IL-13 has also been studied for treatment eosinophilic asthma.[22]

Conclusion

For biological therapy used for treatment of severe asthma, more comparative trials would help us to decide what is more suitable for our individual patients. At the moment, it appears that subjects with eosinophilic severe asthma with these phenotypes: recurrent exacerbations, high serum IgE level, high FeNO level and high blood eosinophil count would benefit from anti-IL5 or anti-IL4 therapy. For subjects with T2 allergic severe asthma with high serum periostin, high serum IgE and high FeNo, anti-IgE, anti-IL13 or anti-IL4 therapy would be helpful.[13] Development of new therapies and further research would certainly benefit severe asthma patients. Personalised therapy for this group of patients can help to decrease their morbidity. Further researches on choosing the correct agent for the patients with specific phenotypes are needed.

References

1. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2007;62:758-66.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2016. Available from: www.ginasthma.org (last accessed date: 13 Jun 2016).
3. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-pacific region. Allergy, asthma & immunology research 2013;5:251-7.
4. Ko FW, Lai CK, Woo J, Ho SC, Ho CW, Goggins W, Hui DS. 12-year change in prevalence of respiratory symptoms in elderly Chinese living in Hong Kong. Respir Med 2006;100:1598-607.
5. British Thoracic Society/Scottish Intercollegiate Guidelines Network asthma guideline. 2014;https://www.brit-thoracic.org.uk/guidelines-and-quality-standards/asthma-guideline (Last accessed date: 13 Jun 2016).
6. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. The European respiratory journal 2014;43:343-73.
7. Licari A, Marseglia G, Castagnoli R, Marseglia A, Ciprandi G. The discovery and development of omalizumab for the treatment of asthma. Expert opinion on drug discovery 2015;10:1033-42.
8. Milgrom H, Fick RB, Jr., Su JQ, Reimann JD, Bush RK, Watrous ML, Metzger WJ. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. The New England journal of medicine 1999;341:1966-73.
9. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. The Cochrane database of systematic reviews 2014:CD003559.
10. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, Eisner MD, Wong DA, Busse W. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Annals of internal medicine 2011;154:573-82.
11. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, Lal P, Arron JR, Harris JM, Busse W. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. American journal of respiratory and critical care medicine 2013;187:804-11.
12. Molimard M, Mala L, Bourdeix I, Le Gros V. Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control. Respiratory medicine 2014;108:571-6.
13. Trivedi A, Pavord ID, Castro M. Bronchial thermoplasty and biological therapy as targeted treatments for severe uncontrolled asthma. The Lancet. Respiratory medicine 2016.
14. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.
15. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, Ortega HG, Pavord ID. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. The New England journal of medicine 2014;371:1189-97.
16. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P. Mepolizumab treatment in patients with severe eosinophilic asthma. The New England journal of medicine 2014;371:1198-207.
17. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. American journal of respiratory and critical care medicine 2011;184:1125-32.
18. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. The Lancet. Respiratory medicine 2015;3:355-66.
19. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, van der Merwe R, Kolbeck R, Molfino NA, Raible DG. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. The Lancet. Respiratory medicine 2014;2:879-90.
20. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, Harris JM, Scheerens H, Wu LC, Su Z, Mosesova S, Eisner MD, Bohen SP, Matthews JG. Lebrikizumab treatment in adults with asthma. The New England journal of medicine 2011;365:1088-98.
21. Hanania NA, Noonan M, Corren J, Korenblat P, Zheng Y, Fischer SK, Cheu M, Putnam WS, Murray E, Scheerens H, Holweg CT, Maciuca R, Gray S, Doyle R, McClintock D, Olsson J, Matthews JG, Yen K. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. Thorax 2015;70:748-56.
22. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, Pirozzi G. Dupilumab in persistent asthma with elevated eosinophil levels. The New England journal of medicine 2013;368:2455-66.

SPIOLTO® Improving experience starts now

Superior improvement in lung function over SPIRIVA®[2-4] & LABA/ICS[5#]

Superior improvement in quality of life over SPIRIVA®[6-7]

Superior COPD symptom reduction over SPIRIVA®[4,6-7]

Superior lung deposition over DPIs & MDIs[8-11] – delivered by RESPIMAT®

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

References : **1.** SPIOLTO® RESPIMAT® Prescribing Information. **2.** Ferguson GT, et al. Adv Ther 2015;32:523-536. **3.** Beeh KM, et al. Pulm Pharmacol Ther 2015;32:53-59. **4.** Buhl R, et al. Eur Respir J 2015;45:969-979. **5.** Beeh KM et al. Int J COPD 2016;11:193-205. **6.** Singh D, et al. Poster presented at the ERS International Congress, Amsterdam, Netherlands, September 26-30 2015: poster PA2958. **7.** Singh D, et al. Respir Med 2015;109:1312-1319. **8.** Dalby R, et al. Int J COPD 2004;283:1-9. **9.** Pitcairn G, et al. Aerosol Med 2005;18(3):264-272. **10.** Ciciliani A, et al. Respiratory Drug Del 2014;2:453–456. **11.** Ciciliani A, et al. Respiratory Drug Del 2015;2:357–362.

Abridged Prescribing Information

SPIOLTO® RESPIMAT® (tiotropium & olodaterol)

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

For detailed information, please refer to full prescribing information.

Boehringer Ingelheim

Boehringer Ingelheim (HK) Ltd.
1504-9 Great Eagle Centre., 23 Harbour Road, Wanchai, Hong Kong
Tel: 2596 0033 Fax: 2827 0162

NEW ONCE-DAILY SPIOLTO® RESPIMAT®
TIOTROPIUM & OLODATEROL

SPO-07-2016-02

COPD Pharmacotherapy Update

Dr Loletta KY SO
Specialist in Respiratory Medicine
President, Hong Kong Thoracic Society

Dr Angus HY LO
Specialist in Respiratory Medicine
Hon. Treasurer, Hong Kong Thoracic Society

Dr Loletta KY SO Dr Angus HY LO

Introduction:

In the past decade, we saw a bloom of new treatments and studies to give COPD management a facelift. More than 30,000 articles related to COPD care have been published. More than a dozen new drugs and novel devices are now available to COPD patients.

While most doctors in the field agree with the management principles of the GOLD document, there are still many practical issues that are left undefined. The present article will give a concise account of key principles and controversies in the pharmacotherapy of COPD management. All non-pharmacological treatments, albeit equally important, are beyond the scope of this article.

Pharmacological treatment: General principle

Bronchodilators are the backbone of COPD management. The aim is to control symptoms, improve quality of life, reduce exacerbation risk and avoid adverse events[1]. They include beta agonists, anticholinergics and theophylline. In genera[1], the inhalation route is preferred to the oral route. All symptomatic patients are usually given short acting bronchodilators to be used on an as-needed basis. For maintenance therapy, long acting bronchodilators (at least 12 hours of action) are more effective than short acting ones.

Many physicians would start with monotherapy and then add-on a bronchodilator from another class when the control is not satisfactory in a more or less stepwise approach. Inhaled corticosteroid (ICS) could be added when FEV1<50% predicted with frequent exacerbations[1,2,3]. ICS is also added for those with Asthma/COPD overlap[1]. However, for more symptomatic or severe patients, starting with combination therapy or even triple therapy is sometimes indicated.

Monotherapy: LABA or LAMA?

When we start a patient on montherapy, the first question we face is whether to choose LABA or LAMA first. Most guidelines including the GOLD document do not favour any one class of bronchodilators to the other. The GOLD document suggests to make the choice based on availability and patient response. A Cochrane review by Kew in 2014[5] comparing long acting inhaled therapy in COPD found similar effects between LABA and LAMA overall.

However, data from efficacy trials might give us a clue. Many of these studies suggest once daily LAMA, e.g. tiotropium is superior to twice daily LABAs, e.g. salmeterol and formotero[l6,7]. Because of these results, many physicians prefer LAMA as the initial therapy over twice daily LABAs a few years ago. This superiority becomes blurred with the introduction of ultra-LABA e.g. indacaterol, olodaterol (24 hours of action) in the market[8,37-38].

Besides, many of these superiority results in efficacy trials appear to be related to the primary outcome sought. For instance, LAMA appears to be more effective than LABA for exacerbation prevention[7,9], while LABA, especially ultra-LABA, appears superior to LAMA in terms of symptom improvement and health related quality of life in some trials[10]. Certainly, such relationships are not universally consistent across all studies, especially for the latter finding in symptom or quality of life, where LAMA also gives favourable response[11].

Nevertheless, it might still be reasonable to start with LABA or LAMA in more symptomatic patients and to start with LAMA in patients with frequent exacerbations.

Combination therapy: LABA+ICS

The GOLD document includes LABA+ICS as the first choice treatment for patients with FEV1 < 50% and at high risk of exacerbations (Group C and D)[1]. The use of such combination is also advisable for any patient suspected to have asthma overlap[1].

LABA+ICS is found to be superior to LABA alone in preventing exacerbations[3,4].

Data from the INSPIRE Study suggest LABA+ICS to be similar in reducing exacerbations as LAMA overall, although there tend to be more exacerbations requiring antibiotics with LABA+ICS while more exacerbations requiring oral steroid with LAMA[4]. Further, a reduction in all cause mortality was observed in the LABA+ICS arm over LAMA. On the other hand, a subsequent analysis of this trial found that pneumonia was more frequent in the LABA+ICS group. A Cochrane review in 2014 suggested ICS (fluticasone and budesonide included) to be associated with increased risk of pneumonia but not the overall mortality[12]. Fluticasone

was associated with a higher risk of pneumonia when compared with budesonide[12]. This result should not be considered conclusive given the variations in the definition of pneumonia among studies and potential confounders.

Apart from the pneumonia risk, ICS, especially in high doses, is associated with increased bone loss and osteoporosis risk in some studies and systemic reviews[13-16]. These findings are not confirmed with a few prospective studies and 1 meta-analysis[13,17-20]. On the other hand, COPD and immobility are also well known to be associated with osteoporosis[1,21]. Thus, the potential risk of ICS should be considered against the proven benefit of its use in COPD patients.

Nevertheless, we should try to limit the use of ICS to those indicated patients and to avoid ICS monotherapy in COPD. Measurement of bone marrow density and measures to prevent osteoporosis should be considered in COPD patients; especially those receiving high dose ICS.

Combination therapy: LABA+LAMA

While many will add a second class of bronchodilators when monotherapy is not satisfactory, some prefer starting dual bronchodilators to COPD patients with significant symptoms or risk. Indeed, LABA+LAMA is included as an alternate treatment choice in the GOLD document for group B to D patients[1].

A recent trial showed LABA+LAMA to be more effective than LABA+ICS in reducing exacerbations among patients with a history of exacerbations during the previous year[22]. Several studies also suggested improved lung function and reduced exacerbations compared with LAMA or LABA alone[23-26]. Thus, dual bronchodilators might further improve the care of COPD patients although its optimal position in relation to existing therapies needs to be better defined with further studies.

Combination therapy: Triple therapy (LABA+LAMA+ICS)

In patients with severe COPD, triple therapy is often used. The benefit of which is first suggested by the UPLIFT trial showing superior lung function and reduced exacerbations compared with two-thirds of patients using LABA+ICS as usual care[27]. These findings are also supported by the CLIMB trial where triple therapy reduced severe exacerbations compared with LAMA alone[28]. However, when and for whom to start with triple therapy and whether the risk of ICS is justifiable remain controversial.

Other treatments

Long term Oxygen therapy is well proven to improve survival and quality of life of hypoxaemic patients with PaO_2 ≤55 mmHg, or those with PaO_2 between 55 – 60mmHg in the presence of evidence of tissue hypoxia[29,30]. Anti-inflammatory therapy, in particular, roflumilast, has been shown to reduce exacerbations together with a modest benefit to lung function[31-33]. It is used as an add-on to other maintenance therapy to prevent exacerbations in high-risk patients, particularly those with chronic bronchitis phenotype. The use of high dose mucolytics[34,35] and long-term antibiotics36 are found to be useful in certain patients. However, their regular use is still under debate and cannot be recommended as standard therapy.

Conclusion

Undoubtedly, there are now major breakthroughs in terms of bronchodilators for COPD patients. More powerful and longer acting drugs are now available to markedly improve symptoms and reduce exacerbations over historic short acting agents. While most of us follow the treatment framework of the GOLD documents, the correct treatment strategy or the order of using various bronchodilators, alone or in combination for different patients remains incompletely defined. Availability and individual clinical response remain the major clues to define treatment at present. More studies on different treatment strategies and head to head comparisons among alternate options are needed to direct optimal therapy in future.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis, Management, and Prevention of COPD 2016. www.goldcopd.org (Accessed on 1st June, 2016).
2. Ferguson GT, Anzueto A, Fei R, et al. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. Respir Med. 2008;102(8):1099.
3. Calverley PM, Anderson JA, Celli B, et al, TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775.
4. Wedzicha JA, Calverley PM, Seemungal TA et al, INSPIRE Investigators. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19.
5. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and sterdois) for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014;10.1002/14651858.CD010844
6. Donohue JF, van Noord JA, Bateman ED, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 2002;122: 47–55
7. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364: 1093–1103.
8. Vogelmeier C, Magnussen H, LaForce C, et al. Profiling the bronchodilator effects of the novel ultra-long-acting b2-agonist indacaterol against established treatments in chronic obstructive pulmonary disease. Ther Adv Respir Dis 2011; 5: 345–357.
9. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallelgroup study. Lancet Respir Med 2013; 1: 524–533
10. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting b-agonists for stable COPD: a systematic review. Chest 2012;142: 1104–1110.
11. Cope S, Donohue JF, Jansen JP, et al. Comparative efficacy of long-acting bronchodilators for COPD – a network meta-analysis. Respir Res 2013; 14: 100.
12. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014; 10: CD010115.
13. Drummond MB, Dasenbrook EC, Pitz MW et al. Inhaled corticosteroid in patiens with stable chronic obstructive pulmonary disease: a systemic review and meta-analysis. JAMA. 2008;300(20):2407
14. Weatherall M, James K, Clay J et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. Clin Exp Allergy. 2008 Sep;38(9):1451-8
15. Etminan M, Sadatsafavi M, Ganjizadeh Zavareh S. et al. Inhaled corticosteroids and the risk of fractures in older adults: a systemic review and meta-analysis. Drug Saf. 2008;31(5):409-14
16. Richy F, Bousquet J, Ehrlich GE et al. Inhaled corticosteroids effects on bone in asthmatic and COPD patients: a quantitative systemic review. Osteoporosis int. 2003 May;14(3):179-90
17. Yang IA, Clarke MS, Sim EH et al. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Sys Rev 2012

18. Hughes JA, Conry BG, Male SM et al. One year prospective open study of the effect of high dose inhaled steroids, fluticasone propionate, and budesonide on bone markers and bone mineral density. Thorax.1999;54(3):223
19. Tattersfield AE, Town GI, Johnell O et al. Bone mineral density in subjects with mild asthma randomized to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax.2001;56(4):272
20. Jones A, Fay JK, Burr M et al. Inhaled corticosteroid effects on bone metabolism in asthma and mild chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2002
21. Van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res 2001;16(3):581
22. Wedzicha JA, Banerji D, Chapman KD et al, FLAME investigators. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med 2016;374:2222-2234
23. Donohue JF, Maleki-Yazdi MR, Kilbride S et al. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respir Med. 2013 Oct;107(10):1538-46
24. Celli B, Crater G, Kilbride S, et al. Once-daily umeclidinium/vilanterol 125/25 mcg in COPD: a randomized, controlled study. Chest. 2014;145(5):981
25. Bateman ED, Chapman KR, Singh D et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res. 2015;16:92. Epub 2015 8 2.
26. Singh D, Jones PW, Bateman ED et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. BMC Pulm Med. 2014;14:178. Epub 2014 11 18
27. Tashkin DP, Celli B, Senn S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359(15):1543.
28. Welte T, Miravittles M, Hernandex P et al. Efficacy and tolerability of Budesonide/Formoterol added to Tiotropium in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009. Oct 15;180(8):741-50
29. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet. 1981;1(8222):681.
30. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93(3):391.
31. Rabe KF, Bateman ED, O'Donnell D et al. Roflumilast--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2005;366(9485):563.
32. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009;374(9691):695.
33. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009;374(9691):685.
34. Tse HN, Raiteri L, Wong KY et al Benefits of High Dose N-Acetylcysteine to Exacerbation-Prone Patients with COPD. Chest 2014,146(3):611-23
35. Zheng JP, Wen FQ, Bai CX et al. Twice daily N-acetylcysteine 600mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomized, double blind placebo-controlled trial. Lancet Respir Med. 2014 Mar;2(3):187-94
36. Albert RK, Connett J, Bailey WC et al. Azithromycin for Prevention of Exacerbations of COPD. N Engl J Med 2011;365:689-98
37. Koch A, Pizzichini E, Hamilton A et al. Lung function efficacy and symptomatic benefit of olodaterol once daily deflievered via Respimat versus placebo and formoterol tweice daily in patients with GOLD 2-4: results from two replicate 48 week studies. Int J Chron Obstruct Pulmon Dis 2014;9:697-714
38. Ferguson GT, Feldman GJ, Hofbauer P et al. Efficacy and safety of olodaterol once daily delivered via Respimat in patients with GOLD 2-4 COPD: results from two replicate 48 week studies. Int J Chron Obstruct Pulmon Dis 2014;9:629-45

PRINCESS CRUISES
come back new℠

SUMMER EXTENSION DEALS

More Singapore Sailings:

CHANGI airport singapore

With over 100 airlines serving more than 300 cities worldwide, Singapore is easily accessible via Changi Airport, a well-connected airhub

All Fares INCLUDE Taxes, Fee & Port Expenses.

3Days Malaysia

Roundtrip from Singapore
Diamond Princess

Singapore | Penang, Malaysia | Kuala Lumpur (Port Kelang), Malaysia | **Singapore**

9Dec2016

Oceanview FREE UPGRADE Balcony

HKD4,555* up

*Obstructed Oceanview

7Days Vietnam & Thailand

Roundtrip from Singapore
Diamond Princess

Singapore | Ko Samui, Thailand | Bangkok (Laem Chabang), Thailand | Ho Chi Minh City (Phu My), Vietnam | **Singapore**

27Jan 福 |
23Feb▲ | 4Mar2017

HKD7,402up

▲This is a 5 days sailing and will not call to Ho Chi Minh City (Phu My), cruise fare is from HKD5,414.

17Days Andes & South America

From Los Angeles to Santiago (Valparaiso)
Crown Princess

Los Angeles, California | Manzanillo, Mexico | San Juan del Sur, Nicaragua | Puntarenas, Costa Rica | Lima (Callao), Peru [Overnight] | Pisco (San Martin), Peru | La Serena (Coquimbo), Chile | **Santiago (Valparaiso), Chile**

Ultimate Sales Less than $545 per day!

4Dec2016

HKD9,236up

14Days Cape Horn Route to Rio

Sail between Rio de Janeiro to Santiago (Valparaiso)
Crown Princess

Rio de Janeiro, Brazil | Buenos Aires, Argentina | Montevideo, Uruguay | Falkland Islands (Stanley) | Cape Horn [Scenic Cruising] | Ushuaia (Tierra del Fuego), Argentina | Punta Arenas, Chile | **Santiago (Valparaiso), Chile**

21Dec2016# 🎄 2017 |
4Jan2017

#Port Order may vary.

HKD12,044up

Promotions are subject to capacity control.

PRINCESS CRUISES come back new℠
2952 8079 | 6898 8919
www.princess.com
Suite 1207, Tower 1, The Gateway, Harbour City
25 Canton Road, Kowloon, Hong Kong

Advances in management of non-cystic fibrosis bronchiectasis

Dr Macy LUI
MBBS(HK), MRCP (UK), FHKCP, FHKAM (Medicine), FCCP
Honorary Clinical Assistant Professor, Department of Medicine, University of Hong Kong

Dr David CL LAM
MBBS(HK), MD(HK), PhD(HK), FHKCP, FHKAM(Medicine), FRCP(Edin & Glasgow), FCCP, FACP
Clinical Assistant Professor, Department of Medicine, University of Hong Kong


Dr Macy LUI Dr David CL LAM

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 September 2016.

Introduction

Bronchiectasis is characterised by abnormal irreversible dilatation of the bronchial trees. While cystic fibrosis(CF) is prevalent in the Caucasian populations, this congenital cause of bronchiectasis is exceptionally uncommon in Chinese.[1] Despite the improvement in the management of pulmonary tuberculosis and respiratory tract infections and implementation of effective vaccination programmes, the crude mortality and hospitalisation rates attributable to bronchiectasis remained relatively static over the years, at 2.7/100,000 and 21.9/100,000 population respectively in 2005.[2] Patients suffering from bronchiectasis are often chronic sputum producers, with recurrent exacerbations or haemoptysis. A vicious cycle of chronic airway infection and inflammation leads to progressive tissue damages, lung function decline and resultant morbidities. Impairment in mucociliary clearance in the damaged airway and mucosa perpetuates further retention of secretion and bacterial growth. Previous management strategies for non-CF bronchiectasis have been extrapolated from literatures on cystic fibrosis, which is, however, a congenital disease with clearly distinct aetiology, pathogenesis, natural course and prognosis as compared to non-CF bronchiectasis. Chest physiotherapy, inhaled bronchodilators and anti-bacterial treatment for exacerbations or as chronic suppression constitute the main strategies for non-CF bronchiectasis, in addition to general measures such as nutrition and vaccination against respiratory infections. Inhaled bronchodilators, including beta-agonists or anti-cholinergics, are frequently prescribed for symptomatic relief especially for subjects with evidence of airflow obstruction on lung function, though their use has recently been linked to a risk of haemoptysis.[3] With more understanding on the pathogenesis of non-CF bronchiectasis, recent studies have examined interventions targeting the key elements involved in the pathogenesis and progression of non-CF bronchiectasis.

Anti-inflammation and immune-modulation

Inhaled corticosteroids (ICS) have been studied for its anti-inflammatory effect in non-CF bronchiectasis. High dose inhaled corticosteroids have been shown to reduce sputum volume, inflammatory markers in sputum and clinical symptoms, but such potential benefits have to be balanced against side effects related to systemic absorption and immunosuppression within the airways.[4] No clear benefits on exacerbation frequency, lung function decline and mortality have been demonstrated in relation to the use of ICS. The role of systemic steroid is mainly limited to specific forms of bronchiectasis such as allergic bronchopulmonary aspergillosis (ABPA).

The immune-modulatory activity of macrolides was first investigated in diffuse panbronchiolitis, a specific type of chronic suppurative lower airway inflammation and bronchiolitis affecting mainly East Asians.[5] Macrolides exert direct a suppressive effect on leukocyte function, expression of pro-inflammatory cytokines by leukocytes and free radicals production, and thus inflammation is attenuated.[6] Macrolides were also reported to reduce airway secretion by modulating mucin gene expression. Interest in the role of macrolides in non-CF bronchiectasis started off with a few small-scale studies. The randomised controlled trial by Koh YY and co-workers including 25 children found an improvement in airway hyper-responsiveness with oral roxithromycin for twelve weeks as compared to placebo.[7] Yalcin and co-workers demonstrated a reduction in sputum inflammatory mediators and daily sputum production but not lung function parameters after clarithromycin for three months, in a group of children with stable-state bronchiectasis.[8] After taking oral erythromycin (500mg bid) for eight weeks, forced expiratory volume in one second, forced vital capacity and daily sputum volume were improved in a local study by Tsang and co-workers.[9] In another cohort of 33 patients with heterogeneous causes of bronchiectasis, a reduction in exacerbation frequency was observed with at least four months' therapy with azithromycin 250mg daily.[10] Three recent large clinical trials provided supports for the immunomodulatory effects of macrolides in reducing exacerbations in non-CF bronchiectasis. In the Effectiveness of Macrolides in patients with Bronchiectasis using Azithromycin to control Exacerbations (EMBRACE) trial, 141 patients were randomised to receive either azithromycin 500mg or placebo three times weekly for six months.[11] A reduction in the rate of exacerbation was seen in the azithromycin group as compared to the placebo group, though no significant effects were noted in lung function and quality of life measures after six months. The anti-bacterial dosage used in that trial has been

scrutinised to contribute partly to the reduction of infective exacerbations. In the Bronchiectasis and Long-term Azithromycin Treatment (BAT) trial, 83 patients with non-CF bronchiectasis were randomised to receive azithromycin 250mg daily or placebo for twelve months. Similar to the EMBRACE trial, patients receiving maintenance azithromycin had fewer exacerbations, while with the longer follow up, improvement in quality of life and FEV_1 were also demonstrated.[12] Despite the common occurrence of gastro-intestinal upset, it was mild and did not necessitate discontinuation of treatment. However, the issue of microbial resistance was one major concern in these studies. Erythromycin, which is believed to be least broad-spectrum and hence poses less selection pressure, was also found to reduce exacerbations, sputum volume and lung function decline in the Bronchiectasis and Low-dose Erythromycin Study (BLESS) trial.[13]

One concern against widespread use of chronic macrolide therapy is the development of bacterial resistance among common respiratory pathogens such as *Streptococcal pneumoniae*, oro-pharyngeal flora and non-tuberculosis mycobacteria.(3 trials) The increased occurrence of hearing impairment and arrhythmias with QT prolongation also raise concerns regarding the safety of long-term macrolides.[14] Based on the current evidence, the use of maintenance macrolide therapy should mainly be restricted to patients with frequent exacerbations despite correction of modifiable risk factors, and with no contraindications such as drug hypersensitivity.

Facilitation of airway clearance

Effective clearance of secretion from the airways is of crucial importance in breaking the vicious cycle of colonisation, infection, inflammation and tissue damage taking place in the airway environment. Postural drainage, to be performed on a daily out-patient basis, has been widely advocated for patients with bronchiectasis. Techniques and devices to facilitate chest physiotherapy, including active cycles of breathing, manual chest percussion, oscillatory positive expiratory pressure (PEP), high frequency chest wall oscillation (The Vest system) have been adopted in previous studies with documented benefits.[4,15] While the current level of evidence does not inform clearly on the superiority of any one technique over the others, postural drainage and specific chest physiotherapy techniques should be tailored to the preference and capability of the patients. Optimal systemic hydration is an often overlooked but important measure to reduce viscosity of sputum and to improve muco-ciliary clearance.[16]

Nebulised hypertonic saline or inhaled mannitol (dry powder) can reduce the osmolarity of airway secretion and improve clearance. Both inhaled hypertonic saline (6%) and normal saline were reported to improve quality of life, forced expiratory volume in one second by 90ml on average, and sputum bacteriology over twelve months in non-CF bronchiectasis.[17] Whether the alteration in the inflammatory profile and immune-modulating effect of nebulised hypertonic saline as observed in cystic fibrosis[18] can be applied to non-CF counterparts would require further dedicated studies.

Inhaled Dornase alfa, recombinant human DNase, was found to be potentially harmful in non-CF bronchiectasis in terms of exacerbation frequency and lung function decline, as opposed to the benefits observed in cystic fibrosis.[19] A recent randomised controlled study including 461 patients with non-CF bronchiectasis found a beneficial effect from inhaled mannitol (400mg twice per day) for 52 weeks in prolonging the time to first exacerbation and improving quality of life, though the primary endpoint on exacerbation rate was not significant.[20]

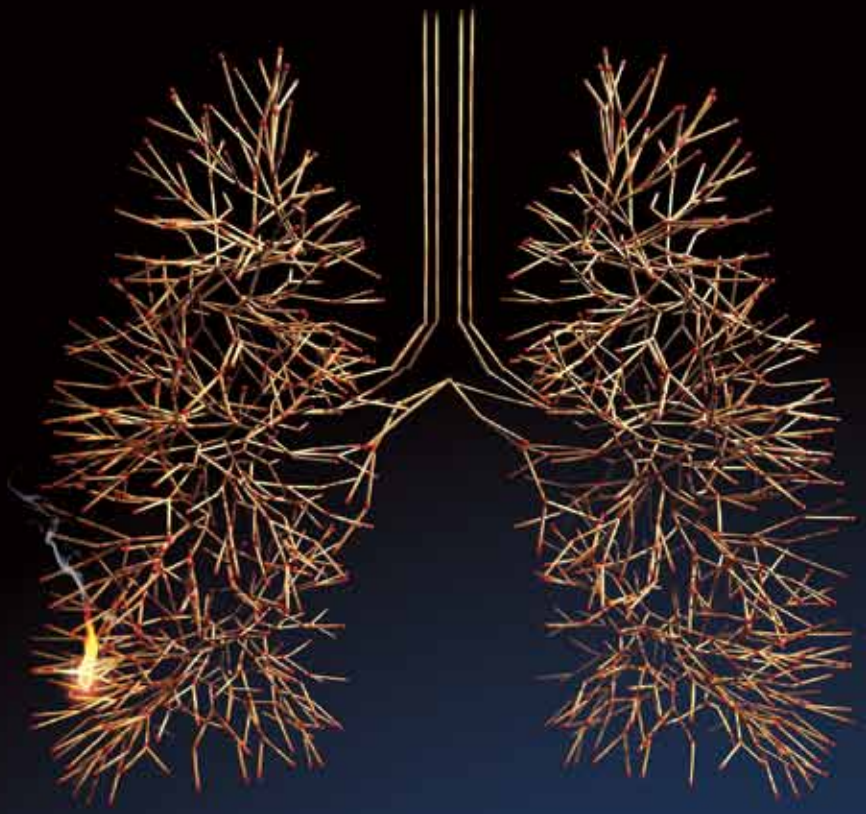
Anti-bacterial therapy

In contrast to the normal lower bronchial trees which are relatively bacteria-free, the dilated bronchi and bronchioles in bronchiectasis are chronically colonised by various bacterial strains, such as Streptococcus, Staphylococcus, Haemophilus or Pseudomonas species.[21] Bacterial load within the lower airways has been shown to be related directly to airway inflammation, systemic inflammation and risk of subsequent exacerbation.[22] Overgrowth of bacteria inside the airways and activated inflammation lead to clinical exacerbations which accelerate tissue damage. In particular, the persistence of *Pseudomonas aeruginosa* (PA) in the airways is associated with more severe disease and accelerated lung function decline (FEV_1) as much as -123ml per year, as compared to -53ml per year in general non-CF bronchiectasis patients or -30ml per year related to ageing.[23] In addition to the adverse impact on lung function, the isolation of PA and lowered body mass index were both significant predictors of radiological progression of non-CF bronchiectasis in a recent cohort study.[24]

Patients presenting with increased sputum purulence, sputum volume, with or without fever or haemoptysis should be treated promptly as with systemic antibiotics, with reference to the results of prior microbiological workup (culture and sensitivity pattern) of respiratory specimen. A course of antibiotics for 10-21 days, depending on the predominant bacteria identified in the sputum and clinical response, is typically required for treatment of exacerbation.[25] As airway colonisation by PA has clearly been shown to be associated with worse prognosis, aggressive antibiotic therapy has been investigated in a few small scale studies in an attempt to eradicate the pathogenic strain. In a retrospective study, systemic anti-Pseudomonas therapy followed by three-months nebulised colistin was associated with a high initial eradication rate (80%) and reduced exacerbations over a median follow up time of two years, but about 50% were 're-infected' by PA after 6 months.[26] In this retrospective series, no impact on lung function was found. A recent 15-months randomised study, 16 patients received nebulised tobramycin was compared to 19 patients who received nebulised placebo, both groups were colonised by PA and had received 14-days intravenous ceftazidime and tobramycin prior to the study. The number of exacerbations and hospitalisations were lower in the tobramycin group over the study period. Of note, the result was affected by a high early drop-off rate in the treatment group and up to a third of the treatment group was affected by bronchospasm.[27] Further studies are needed to investigate the value of PA eradication in non-CF bronchiectasis patients, the

Exacerbations tend to cluster in time[1]

Add Daxas® before one exacerbation leads to another



The only oral selective PDE4 inhibitor for COPD patients with chronic bronchitis with a history of frequent exacerbations[2]:

- Controls lung inflammation[2-4]
- Reduces about ¼ of severe exacerbations and hospital admissions in severe COPD patients on appropriate combination therapy[3,4]
- Improves lung function and reduce the use of rescue medication[3,4]
- Generally well tolerated[3,4]

Abbreviated Prescribing Information:

Presentation: Roflumilast 500 micrograms film-coated tablet. Indication: Maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV$_1$ post bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. Dosage: One 500 micrograms tablet once daily. Daxas tablet with water, with or without food, at the same time every day. May need several weeks to achieve its beneficial effect. Contraindications: Hypersensitivity to roflumilast or any of its excipients, moderate or severe hepatic impairment. Precautions: Should not be used in patients with acute bronchospasm, severe immunological diseases, severe acute infectious diseases, cancers, ignorance intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption, in patients treated with immunosuppressive drugs, and in patients during breastfeeding. Not recommended in patients with congestive heart failure, history of depression associated with suicidal ideation or behaviour, concomitant theophylline treatment, in patients of childbearing potential not using contraception or during pregnancy, and in patients receiving strong cytochrome P450 enzyme inducers. Cautious use in patients with mild hepatic impairment. Should monitor weight, psychiatric symptoms, and persistent intolerability in patients on CYP1A2/CYP3A4 inhibitors or CYP1A2/3A4 inhibitor enoxacin. Interactions: Fluvoxamine, cimetidine, fluconazole, erythromycin, ketoconazole, theophylline, and oral contraceptive containing gestodene and ethinyl oestradiol increase total PDE4 inhibitory activity; rifampicin, phenobarbital, carbamazepine and phenytoin reduce total PDE4 inhibitory activity. Undesirable effects: Weight decrease, decreased appetite, insomnia, headache, diarrhoea, nausea, abdominal pain. Full local prescribing information is available upon request. API-HK-DAX-0815

References: 1. Hurst JR, et al. *Am J Respir Crit Care Med*. 2009;179:369-374. 2. Daxas Prescribing Information 2015. 3. Martinez FJ, et al. *Lancet* 2015;385:857-66. 4. Wedzicha JA et al. *Int J COPD* 2016; 11: 81-90.

PDE4 inhibitor : phosphodiesterase-4 inhibitor

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

Daxas is a registered trademark of AstraZeneca group of companies

Daxas® roflumilast

Further information is available on request

AstraZeneca Hong Kong Limited
18/F, Shui On Centre, 6-8 Harbour Road,
Wanchai, Hong Kong
Tel: (852)2420 7388 Fax: (852)2422 6788

AstraZeneca 阿斯利康

API-HK-DAX-0815 Aug 15

way to achieve a sustainable eradication and to identify any subgroup of patients, for whom eradication therapy may be beneficial.

For those who fail eradication, a prolonged course of inhaled antibiotics provides a practical option to suppress the bacterial burden and to prevent exacerbations. Inhalation of nebulised antibiotics has been shown to result in high concentrations achieved inside the airways with more effective bacterial suppression while lessening the risk of systemic side effects. Several pieces of work have supported the use of inhaled antibiotics, such as tobramycin and colomycin, in non-CF bronchiectasis, with reductions in the bacterial load of Pseudomonas species and in the exacerbation rates.[28-31] A recent randomised controlled study, including 65 patients with non-CF bronchiectasis, has shown that nebulised gentamicin (80mg twice per day) for twelve months was associated with reductions in the bacterial density and fewer exacerbations.[32] A Phase 2 multicentre randomised controlled trial (ORBIT-2) on the use of dual-release liposomal ciprofloxacin, which is administered once daily by nebulisation in a 28 days on and 28 days off schedule, has demonstrated a reduction in Pseudomonas density, prolongation of the time to first exacerbation and good tolerance to treatment.[33] A phase 3 randomised double-blind, placebo-controlled, multicentre study (RESPIRE 2) of inhaled dry power ciprofloxacin in non-CF bronchiectasis is currently ongoing.

Summary

Other than asthma and chronic obstructive pulmonary disease, non-CF bronchiectasis represents another major airway disease causing secondary pulmonary and systemic complications, with far-reaching impacts on morbidities, health care utilisation and economic loss. Tremendous efforts haves been made in recent decades to uncover the pathogenesis and to explore specific treatment for non-CF bronchiectasis, leading to a major shift in the paradigm of management. More high quality and adequately powered studies are awaited to inform the proper management of non-CF bronchiectasis in the future.

References

1. Tian X, Liu Y, Yang J, Wang H, Liu T, Xu W, et al. p.G970D is the most frequent CFTR mutation in Chinese patients with cystic fibrosis. Hum Genome Var. 2016;3:15063.
2. Chan-Yeung M, Lai CK, Chan KS, Cheung AH, Yao TJ, Ho AS, et al. The burden of lung disease in Hong Kong: a report from the Hong Kong Thoracic Society. Respirology. 2008;13 Suppl 4:S133-65.
3. Jang EJ, Lee CH, Yoon HI, Kim YJ, Kim JM, Choi SM, et al. Association between inhaler use and risk of haemoptysis in patients with non-cystic fibrosis bronchiectasis. Respirology. 2015;20(8):1213-21.
4. McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine. 2013;188(6):647-56.
5. Lin X, Lu J, Yang M, Dong BR, Wu HM. Macrolides for diffuse panbronchiolitis. Cochrane Database Syst Rev. 2015;1:CD007716.
6. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. The European respiratory journal. 2013;42(1):239-51.
7. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. The European respiratory journal. 1997;10(5):994-9.
8. Yalcin E, Kiper N, Ozcelik U, Dogru D, Firat P, Sahin A, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. Journal of clinical pharmacy and therapeutics. 2006;31(1):49-55.
9. Tsang KW, Chan WM, Ho PL, Chan K, Lam WK, Ip MS. A comparative study on the efficacy of levofloxacin and ceftazidime in acute exacerbation of bronchiectasis. The European respiratory journal. 1999;14(5):1206-9.
10. Davies G, Wilson R. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. Thorax. 2004;59(6):540-1.
11. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380(9842):660-7.
12. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA : the journal of the American Medical Association. 2013;309(12):1251-9.
13. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA : the journal of the American Medical Association. 2013;309(12):1260-7.
14. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. The New England journal of medicine. 2011;365(8):689-98.
15. Feldman C. Bronchiectasis: new approaches to diagnosis and management. Clinics in chest medicine. 2011;32(3):535-46.
16. Randell SH, Boucher RC, University of North Carolina Virtual Lung G. Effective mucus clearance is essential for respiratory health. American journal of respiratory cell and molecular biology. 2006;35(1):20-8.
17. Nicolson CH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respiratory medicine. 2012;106(5):661-7.
18. Reeves EP, Williamson M, O'Neill SJ, Greally P, McElvaney NG. Nebulized hypertonic saline decreases IL-8 in sputum of patients with cystic fibrosis. American journal of respiratory and critical care medicine. 2011;183(11):1517-23.
19. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. Chest. 1998;113(5):1329-34.
20. Bilton D, Tino G, Barker AF, Chambers DC, De Soyza A, Dupont LJ, et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax. 2014;69(12):1073-9.
21. Rogers GB, van der Gast CJ, Cuthbertson L, Thomson SK, Bruce KD, Martin ML, et al. Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota composition. Thorax. 2013;68(8):731-7.
22. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine. 2012;186(7):657-65.
23. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, Roman-Sanchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest. 2007;132(5):1565-72.
24. Park J, Kim S, Lee YJ, Park JS, Cho YJ, Yoon HI, et al. Factors associated with radiologic progression of non-cystic fibrosis bronchiectasis during long-term follow-up. Respirology. 2016.
25. O'Donnell AE. Bronchiectasis: which antibiotics to use and when? Current opinion in pulmonary medicine. 2015;21(3):272-7.
26. White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis. Respiratory medicine. 2012;106(3):356-60.
27. Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration. 2015;90(4):299-305.
28. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. American journal of respiratory and critical care medicine. 2000;162(2 Pt 1):481-5.
29. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. Chest. 2005;127(4):1420-6.
30. Drobnic ME, Sune P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. The Annals of pharmacotherapy. 2005;39(1):39-44.
31. Dhar R, Anwar GA, Bourke SC, Doherty L, Middleton P, Ward C, et al. Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with Pseudomonas aeruginosa. Thorax. 2010;65(6):553.
32. Murray MP, Govan JR, Doherty CJ, Simpson AJ, Wilkinson TS, Chalmers JD, et al. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine. 2011;183(4):491-9.
33. Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. Thorax. 2013;68(9):812-7.

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Advances in management of non-cystic fibrosis bronchiectasis" by Dr Macy LUI and Dr David CL LAM and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 September 2016. 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. **Cystic fibrosis is a significant cause of the mortality and hospitalisation rates in Hong Kong over the past years.**
2. **High dose inhaled corticosteroids can reduce sputum volume and exacerbation frequency, improve lung function decline and reduce mortality in patients with non-CF bronchiectasis.**
3. **Macrolides (e.g. azithromycin and erythromycin), when being administered in immune-modulatory dosages, had been shown to reduce sputum volume, improve lung function and reduce risk of exacerbation in patients with non-CF bronchiectasis.**
4. **Immuno-modulatory effect on neutrophils and reduced airway secretion through inhibition of mucin gene expression are the underlying mechanisms accounting for clinical effectiveness of macrolides.**
5. **The main adverse effects associated with long term use of Macrolides include alternation of oro-pharyngeal bacterial flora, hearing impairment and prolonged QT interval on ECG.**
6. **Postural drainage should be advocated for patients with bronchiectasis to improve sputum clearance, to reduce bacterial colonisation/ infection, and to minimise airway inflammation and tissue damage.**
7. **Colonisation of lower airways by Pseudomonas aeruginosa is associated with less severe disease and less lung function decline.**
8. **Nebulised aminoglycoside (such as tobramycin) can reduce the number of exacerbations and hospitalisations in non-CF bronchiectasis patients with and without colonisation by Pseudomonas aeruginosa.**
9. **Nebulised antibiotics such as gentamycin and ciprofloxacin can be tried to reduce the density of colonisation by Pseudomonas species and to reduce infective exacerbations in bronchiectasis patients who failed to have Pseudomonas eradicated.**
10. **The option of antibiotics prescribed for treatment of infective exacerbations of bronchiectasis should be considered based on the previous bacterial culture results of lower respiratory specimen.**

ANSWER SHEET FOR SEPTEMBER 2016

Please return the completed answer sheet to the Federation Secretariat on or before 30 September 2016 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Advances in management of non-cystic fibrosis bronchiectasis

Dr Macy LUI
MBBS(HK), MRCP (UK), FHKCP, FHKAM (Medicine), FCCP
Honorary Clinical Assistant Professor, Department of Medicine, University of Hong Kong

Dr David CL LAM
MBBS(HK), MD(HK), PhD(HK), FHKCP, FHKAM(Medicine), FRCP(Edin & Glasgow), FCCP, FACP
Clinical Assistant Professor, Department of Medicine, University of Hong Kong

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

Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

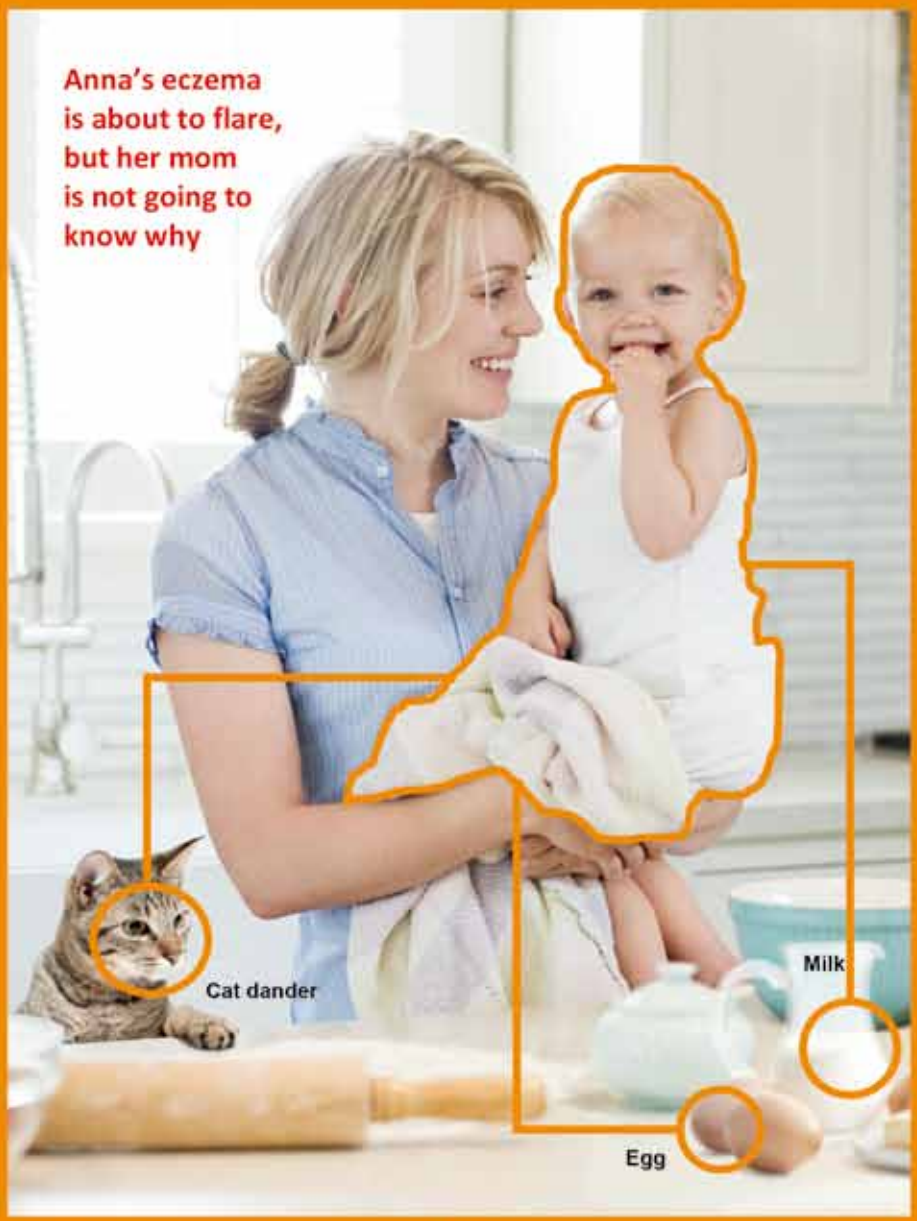
HKID No.: __ __ - __ __ __ __ X X (X) HKDU No.: _____ HKAM No.: _____

Contact Tel No.:_____ MCHK No.: _____ (for reference only)

Answers to August 2016 Issue

Childhood myopia: update on effective prevention

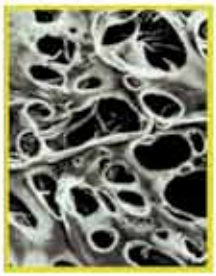
1. F 2. T 3. F 4. T 5. T 6. T 7. F 8. T 9. T 10. T



Discover th

Ecz

Imm
and



ImmunoCAP technology:
Excessive allergen componer
covalently bound to the high
capacity, 3-dimensional cellu
polymer to give reliable resu

Contact of ThermoFisher S
Hotline: 3192-7740
Fax: 2567-4447
Email: sales.hk@thermofis

More than a dozen of quality
ImmunoCAP blood testing, p

ImmunoCAP®
Is it allergy?

ne Connection between **Allergy** and

zema / Rhinitis / Asthma / Gastrointestinal symptoms

mmunoCAP blood testing helps you identify allergy triggers
l develop a management plan for improved patient well-being

nts are

lose
lts.

Why ImmunoCAP

- Recognized as **Gold Standard** for *in vitro* IgE testing
- Published in over **4,000 medical journals**
- The only technology mentioned in Guidelines (CLSI, EAACI, NIH/ NIAID etc.)
- FDA cleared, CE-IVD marked
- Production is ISO 13485 & GMP certified
- Standardized to WHO IgE reference 75/502
- Sophisticated ImmunoCAP technology and fully automated system gives precise and accurate results: proven in extensive researches and external quality assessment programs (CAP, UKNeqas etc.)
- The broadest allergen coverage, including allergen components
- Over 3,000 laboratories worldwide are using ImmunoCAP
- **Dedicated to allergy testing**: Detailed information of every ImmunoCAP allergen can be found in our professional website:

thermoscientific.com/phadia

cientific Hong Kong Office:

sher.com

laboratories in Hong Kong are offering
lease contact us for further information.

Thermo
SCIENTIFIC
Part of Thermo Fisher Scientific

Dermatological Quiz

Dr Lai-yin CHONG

MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)

Specialist in Dermatology & Venereology

Dr Lai-yin CHONG

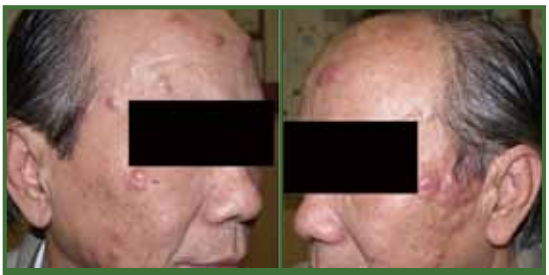


Fig.1: Multiple pinkish nodules on the face

Fig.2: Individual infiltrated lesion has smooth and intact surface

A 60-year-old man presented with a one-year history of multiple asymptomatic pinkish infiltrated nodules on his face (Fig.1). The lesions had smooth and intact surface (Fig.2) and never had ulceration or bleeding. In the past few months, the lesions remained static in size and number. So far there were no systemic symptoms and no lymphadenopathy. His general condition remained well. His past health was good.

Questions

1. What are the clinical differential diagnoses of his skin lesions?
2. What investigations will you order to establish the diagnosis?
3. After clinico-pathological correlation, what is the most important diagnosis that must be excluded first?

(See P.36 for answers)

Non-invasive ventilation for COPD- Hospital and Home Use

Dr P S CHEUNG
FHKAM
Specialist in Respiratory Medicine

Dr C M CHU
MD, FRCP (Lond, Edin, Glasg)
Specialist in Respiratory Medicine


Dr P S CHEUNG Dr C M CHU

Over the last decade, there has been a paradigm shift in the treatment of respiratory failure secondary to airway disease, mostly chronic obstructive airway disease (COPD). Apart from drug treatment, non-invasive ventilation (NIV) has attained an irreplaceable role in the management of hypercapnic respiratory failure both in the acute and chronic phases of severe COPD patients. Severe COPD patients can present acutely with hypercapnic respiratory failure (AHcRF) with severe respiratory distress and impending respiratory arrest. On arrival to hospital, COPD patients shall be first started on standard medical therapy with judicious use of oxygen therapy to achieve oxygen saturation from 88-92%. Patients shall then be put on NIV if the arterial blood pH is below 7.35mmHg & $PaCO_2$ > 45 mmHg after 1 hour of standard medical treatment. The uses of NIV in these patients are well proven by meta-analysis to improve arterial blood gases (ABG), reduce length of hospital stay, ICU stay, intubation and mortality[1]. The use of NIV are however contraindicated in the following conditions-

1. Unstable Haemodynamics
2. Facial distortion due to burn, trauma or recent surgery
3. High aspiration risk due to repeated vomiting or copious sputum
4. Undrained pneumothorax
5. Recent gastrointestinal surgery or suspected intestinal obstruction

In contrast to older believes, recent evidence actually suggests that liberal use of oxygen with NIV may have detrimental effects. Therefore, cautious oxygen supplement aiming to saturation 88-92% is advised. Improvement in arterial pH may be evidence as early as blood gas taken 1 hour after NIV usage. A failing arterial pH, rising carbon dioxide, worsening tachypnoea or desaturation are signs of NIV failure, which should trigger a search for patient-ventilator asynchrony, inappropriate ventilator setting or interface failure.

In intubated and mechanically ventilated COPD patients, NIV also facilitates early weaning from mechanical ventilation, with shorter ICU stay, reduced incidence of ventilator associated pneumonia and lower 60-day mortality[2]. In a COPD patient who has survived an AHcRF, he/she shall be started on rehabilitation when stabilised. NIV improves dyspnoea and exercise tolerance when applied during exercise training[3-4] by prolonging the duration of exercise-induced lactataemia[5], and maybe a useful adjunct in pulmonary rehabilitation.

While most COPD patients survive acute respiratory failure, some cannot. NIV may be used as the ceiling of treatment in COPD patients with acute respiratory failure who refused intubation, if the patients accept that they will have high rates of subsequent mortality and recurrent respiratory failure[6]. However, there are no data to support its routine use for palliative intent at present.

The underlying pathophysiology for chronic type II (hypercapnic) respiratory failure (CHRF) is alveolar hypoventilation, which is attributed by an unfavourable respiratory mechanics due to the hyperinflated chest, presence of intrinsic PEEP (positive end expiratory pressure) and cellular enzymatic down-regulation due to chronic inflammatory, immobilisation state in COPD patients. Over the past two decades, there is an ongoing debate on whether NIV should be useful in COPD patients with CHRF. Early small short-term RCTs on NIV were focused on the physiological effect; which the NIV treated group demonstrated an improvement in gas exchange and health-related quality of life (HQOL)[7-9]. Optimists then conducted RCTs aiming to convert the physiological benefit into patient's survival; however, the early results were disappointing[10-12]. These RCTs could not establish a convincing positive effect on reducing hospital readmission nor improve long term survival. Some authorities refer these early RCTs as "low intensity NIV" as the mean ventilator inspiratory positive airway pressure (IPAP) settings in these studies were ranging from 10 to 18cmH_2O. As mentioned earlier, the root cause for CHRF is the reduced alveolar ventilation which manifested as increased $PaCO_2$. NIV augments nocturnal ventilation, improves alveolar ventilation and reduces the hypercapnia. Struik et al showed that IPAP levels of <18 cmH_2O are not sufficient to achieve a reduction of elevated $PaCO_2$ levels[13]. Therefore, the relative low IPAP setting in these "low intensity NIV" RCTs have been cited to be insufficient to alleviate the alveolar hypoventilation and thus have no significant impact on the altered physiological state in these chronic hypercapnic patients.

In an RCT performed by our team, we randomised 47 patients to receive NIV (n=23) or sham NIV with CPAP 5 cmH_2O (n=24) following an exacerbation of COPD requiring acute NIV, with all patients demonstrating persistent hypercapnia at randomisation[14]. Most of the patients had prior history of AHRF in the past. The

primary end point was respiratory deterioration due to hypercapnic exacerbation, defined as the requirement for NIV in the sham CPAP arm, or escalation of NIV to greater than 12 h/day in the NIV arm. Our study showed a significant benefit of NIV compared to sham treatment for the primary outcome, although the trial did not achieve its planned sample size and this had limited the clinical impact of the findings.

A similar study was performed by the Dutch group. In the RESCUE study, COPD patients with prolonged hypercapnia after ventilator support for acute respiratory failure were randomised to receive NIV or standard treatment[15]. The study failed to reach its primary end point of prolonging the time interval for hospital readmission for respiratory cause or death in the following 12 months despite a significant improved daytime $PaCO_2$ as well as the transcutaneous PCO_2 during the night. The contradiction of study outcomes from these two studies may be explained by the difference in patient selection. The RESCUE study recruited patients with borderline hypercapnia (PCO_2 > 6kPa) at early stage of recovery from acute HCRF, and therefore, not all study objects might have persistent, chronic hypercapnic respiratory failure at randomisation. In our study, most of our patients had history of AHRF and hence these patients were at high risk to develop further AHRF. Combing these two findings, patients with chronic hypercapnic respiratory failure may benefit from NIV if they have persistent hypercapnia. NIV may not be beneficial for those who have resolving respiratory failure after an acute AECOPD. Therefore, the clinician shall defer the eligibility assessment of home NIV for a few weeks when these patients are out of the acute AHRF stage.

A German group has performed another important study of long-term NIV with a marked difference in the study protocol and primary outcome compared with the above two studies. Kohnlein et al performed a prospective, multicentre, randomised, controlled clinical trial enrolled stable GOLD stage IV COPD patients with a partial $PaCO_2$ of 7kPa or higher[16]. Patients were randomly assigned into 1:1 ratio to continue optimised standard treatment or to receive additional NIV for at least 12 months. The primary outcome was the 1-year all-cause mortality. The uniqueness of this study is that the NIV was targeted to reduce baseline $PaCO_2$ by at least 20% or to achieve $PaCO_2$ values lower than 6.5kPa. This reduction was achieved by a combination of increasing IPAP level (mean IPAP 21.6 cmH_2O, mean EPAP 4.8cmH_2O) and the backup rate (mean backup rate 16.1 ± 3.6). The study showed a substantial improvement in survival (1-year mortality in the NIV group was 11.8% vs 33.3% in the control group) and also HQOL in the intervention group.

The concept of using higher IPAP setting was also mentioned in a recently undated meta-analysis by Struik[13]. This meta-analysis concluded that there is currently insufficient evidence to support the application of routine NIV in stable COPD patients, since no significant differences were found between the NIV and control groups after 3 or 12 months of follow-up when looking at $PaCO_2$, 6-minutes walking distance, HROL, lung function and sleep efficiency. However, Struik et al identified those subgroups of higher IPAP levels, better compliance and high baseline $PaCO_2$ levels; the application of NIV seemed to improve elevated $PaCO_2$. The concepts of using more aggressive approach by using a higher IPAP with or without higher respiratory rate have evolved. Some authorities refer it as "High intensity NIV".

Perhaps it is time to update our practice on prescribing NIV to stable COPD patients. Generally speaking, after a hypercapnic respiratory failure, NIV should not be initiated during the same admission; instead, the patient should be reassessed in a few weeks' time after discharge. If there is persistent hypercapnia (> 7kPa), home NIV can be considered for survival benefit. The aim of home NIV treatment would be a significant reduction in $PaCO_2$ level, targeting at normocapnic level because effective NIV can improve survival and HQOL only when pCO_2 is reduced. To achieve this normocapnic state, a higher IPAP level or sometimes a higher backup rate may be needed. In practical terms, we shall see the patients a few weeks after discharge of an AHRF. If there is chronic, significant hypercapnia, we can admit the patient and start home NIV titration. Start with a low level of IPAP and up-titrate gradually until there is a significant reduction in $PaCO_2$, usually IPAP 20-30cmH_2O will be needed. Preferably the backup rate is set just above the patient's spontaneous rate to achieve controlled ventilation. Several RCTs are underway and hopefully we can have more evidence in the near future.

Conclusions

NIV is indispensable in the modern management COPD. In acute hypercapnic respiratory failure, NIV is now the mainstay of ventilatory support. It also has a useful role in bridging invasively ventilated patients to early extubation and weaning from the ventilator. In pulmonary rehabilitation, NIV has an adjuvant role in prolonging exercise training. In persistent hypercapnic respiratory failure, high-intensity home NIV is associated with a survival benefit. Hypercapnic COPD patients in both the acute and chronic settings should receive assessments from respiratory specialists to determine if NIV is beneficial.

References

1. Lightowler JV, Wedzicha JA, Elliot MW, et al. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 2003 326:185.
2. Nava, S, Ambrosino, N, Clini, E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized controlled trial. Ann Intern Med 1998;128:721-728.
3. Keilty SE, Ponte J, Fleming TA, Moxham J. Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. Thorax 1994;49:990-994.
4. Dolmage TE, Goldstein RS. Proportional assist ventilation and exercise tolerance in subjects with COPD. Chest 1997;111:948-954.
5. Polkey MI, Hawkins P, Kyroussis D, et al. Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD. Thorax 2000;55:547-549.
6. Chu CM, Chan VL, Wong IWY, et al. Non-invasive ventilation in patients with acute hypercapnic exacerbation of chronic obstructive pulmonary disease who refused endotracheal intubation. Crit Care Med 2004; 32:372-7.
7. Strumpf DA, Millman RP, Carlisle CC, etal. Nocturnal positive-pressure ventilation via nasal mask in patients with severe chronic obstructive pulmonary disease. Am Rev Respir Dis 1991; 144:1234-1239.

8. Gay PC, Hubmayr RD, Stroetz RW. Efficiency of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clin Proc 1996; 71:533-542.
9. Meecham Jones DJ, Paul EA, Jones PW, et al. Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 1995; 152:538-44.
10. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 2000; 118:1582-1590.
11. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 2002; 20:529-538.
12. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax 2009;64:561-6.
13. Struik FM, Lacasse Y, Goldstein RS, Kerstjens HA, Wijkstra PJ, et al. Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta analysis. Respir Med. 2014 Feb; 108(2):329-37.
14. Cheung AP, Chan VL, Liong JT, Lam JY, Leung WS, Lin A, Chu CM. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2010 May;14(5):642-9.
15. Struik FM, Sprooten RT, Kerstjens HA, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure : a randomised, controlled, parallel-group study. Thorax 2014 ;69 :826-34.
16. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014;2:698-705.1. Nava, S, Ambrosino, N, Clini, E, et al.

OLYMPUS

Your Vision, Our Future

EVIS LUCERA ELITE

Main Features

Extremely-slim-design videoscope

Insertion tube rotation function

Wider angulation range

EVIS LUCERA ELITE BRONCHOVIDEOSCOPE

BF-XP290

Extremely slim, 3.1 mm diameter videoscope reaches further for observation of thinner bronchi

OLYMPUS HONG KONG AND CHINA LIMITED
L43, Office Tower, Langham Place, 8 Argyle Street, Mongkok, Kowloon, Hong Kong
Tel : 2170 5678 Fax : 2170 5679

www.olympusmedical.com.hk

Interventional Pulmonology for Obstructive Airway Diseases

Dr Johnny Wai-man CHAN

MBBS(HK), MRCP(UK), MSc(RespMed)(Lond), MHA(NSW), FRCP(Edin, Glasg & Lond), FHKCP, FHKAM(Med)

Chief of Service and Head of Respiratory Division, Department of Medicine, Queen Elizabeth Hospital

Introduction

Inhaled therapies, including short- and long-acting bronchodilators and corticosteroids, have been the mainstay therapy for obstructive airway diseases such as asthma and chronic obstructive pulmonary disease. However, severe cases which are not adequately controlled with conventional inhaled and oral treatment options have not been infrequently encountered. In recent years, interventional therapeutic options via the bronchoscopic route have emerged as potential alternatives for the moderate-to-severe cases in the medical literature.

Bronchial Thermoplasty (BT) in asthma

The airway obstruction that leads to observed symptoms of asthma like cough, wheezes and shortness of breath is the result of multiple factors. Apart from airway inflammation and mucus hyper-secretion, airway smooth muscle (ASM) contraction is also a prominent feature in asthma[1], and which is associated with the observed histological picture of ASM hypertrophy and hyperplasia of ASM cells in asthmatic airways.[2] Attempting to reduce ASM mass and improve airway calibre had been tested in an animal study with the delivery of radio frequency (RF) thermal energy to canine airways, and which was associated with improvement of airway hyper-responsiveness after the RF ablation.[3]

In human beings, BT is being delivered to the airways with the introduction of a special single-use catheter via the working channel of a usual flexible bronchoscopy. An expandable 4-prong basket is located at the distal end of the catheter, through which contact is made to the airway walls and thermal energy at 65^{0}C for 10 seconds is delivered to the target sites.[4] (Fig.1) The catheter is connected to a RF controller of the system, while a foot switch is being used to initiate the RF activation from the controller. A complete BT therapy consists of 3 separate bronchoscopic sessions, beginning with each lower lobe for the first 2 sessions and completed with treatment of both upper lobes in the last session. The right middle lobe, with its inherent narrow calibre, is not treated in order to avoid any possible permanent damage that leads to stenosis afterwards.[5] Treatment is carried out to the visible portions of the bronchial tree inside the target lobe(s) in a retrograde manner from the distal parts. While the earlier literature had described the use of general anaesthesia in BT, the use of local anaesthesia and conscious sedation has been increasingly described with such procedures, which take usually less than an hour in each session.[6] Reported adverse respiratory events had been usually mild and transient, which included dyspnoea, wheezing, cough and chest discomfort in the early post-treatment period. BT is contraindicated for patients with implanted electronic devices such as pacemakers, as well as those who cannot tolerate the procedure itself or procedural medications required in bronchoscopy.[6]

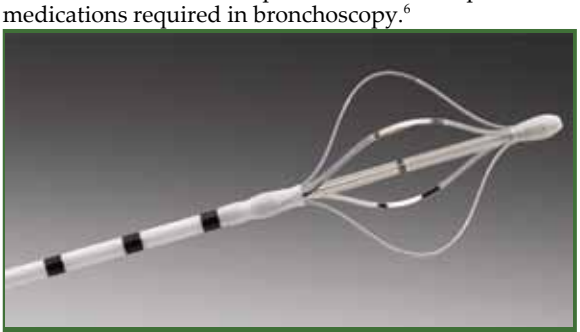


Fig. 1. The BT catheter with an expandable "basket" with 4 electrodes at its tip.

The first BT clinical trial[7] , which was carried out in mild to moderate asthmatic patients, revealed that BT is well-tolerated and can bring about increases in symptom-free days and improvements in airway responsiveness and peak flow readings at 12-weeks when compared to the baseline. Both the subsequent AIR[8] and RISA[9] trials were randomised controlled trials (RCT) on moderate to severe asthmatics. While there were significant improvements in asthma symptoms and quality of life measures, observed improvements in lung function parameters or airway hyper-responsiveness were at most minimal. The AIR-2 trial[10], which was a multi-centre, double-blind, sham-controlled randomised trial on severe asthmatics, revealed improvement in asthma quality of life score, as well as significant reductions in exacerbations, emergency room (ER) visits and days lost from school or work. Follow-up data up to 5 years from such studies have been recently published[11-13], which revealed no deterioration of lung function and no structural changes after BT. On the other hand, the initial benefits after BT, such as the decrease in hospitalizations and ER visits, as well as the reductions in exacerbations, were still observed at 5 years from the RISA and AIR-2 follow-up data. [12, 13]

BT has been approved by the United States Food and Drug Administration (FDA) in 2010 and it had been described in the 2016 updated Global Initiative for Asthma (GINA) guidelines as a "potential treatment

option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimised therapeutic regimens and referral to an asthma specialty centre".[14] However, it should be noted that asthmatic patients with FEV1<50-60% predicted had been excluded in the clinical trials and hence case selection for BT should be careful.[6] Also, performing flexible bronchoscopy in an asthma patient could be a challenging task with the possible bronchoconstriction and presence of mucus hyper-secretion in the airways. On the other hand, the relatively small number of studies and study subjects, as well as the lack of longer term data on the risk and benefit profiles, are factors to be considered before BT can be applied in a more general manner to asthma patients.[15] Lastly, apart from reducing the ASM mass, the precise mechanisms with which BT improves asthma control are still not certain, although some evidence revealed a possible immunomodulatory role for ASM in asthma.[16]

Endoscopic Lung Volume Reduction for Emphysema

Although no longer being included in the current definition of chronic obstructive pulmonary disease (COPD), emphysema is a pathological term to describe the destruction of the gas exchanging alveolar surfaces inside the lungs.[17] Apart from contributing to the observed airflow obstruction in COPD with the loss of elastic recoil and alveolar support, the resulting pulmonary hyperinflation, air trapping and ventilation/perfusion (V/Q) mismatch would also compromise the optimal functioning of the lungs and diaphragm.

Lung volume reduction surgery (LVRS), via surgical resection of emphysematous lung, had been shown to be able to improve overall survival, symptoms and exercise tolerance, particularly in patients with predominant upper lobe disease and low exercise capacity.[18,19] However, LVRS had been associated with significant morbidity and mortality[19] and had only been performed very infrequently.[20]

A number of pulmonary interventions via the bronchoscopic route had been tried to resemble the volume reduction effect offered in LVRS, albeit in a minimally invasive manner. Endobronchial valves (EBV) is the best studied form of bronchoscopic lung volume reduction (BLVR) method[21] and the only device clinically available in Hong Kong at the moment. EBVs are one-way valves that are placed to target diseased segments bronchoscopically, and which block the airflow to such segments during inspiration in order to create lobar atelectasis in the target lobe(s). (Fig.2 and 3) While an earlier RCT[22] can only produce modest effects on lung functions, symptoms and exercise tolerance, subsequent studies revealed that complete (>90%) interlobar fissures from computed tomography[23] and the absence of collateral flow measured bronchoscopically with the Chartis® Pulmonary Assessment System (Pulmonx)[24] can predict responders more accurately before and during the procedure. In a recent study, a responder rate up to 75% has been achieved with such a combined assessment protocol utilised for subject recruitment, and with statistical improvements in lung function parameters (FEV1 and FVC), exercise capacity (6 min walking distance) and dyspnoea scores.[25] Reported complications with EBV implantations include COPD exacerbations, pneumonia, pneumothorax, valve migration and haemoptysis.[21] Replacement or removal of EBVs had been required in up to 15%[25] and pneumothorax has been described in up to 20% in a series.[26]

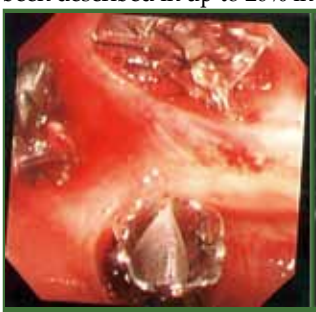


Fig. 2. Three Endobronchial valves being deployed in right upper lobe of a patient's lung (bronchoscopic view)

Fig. 3. Endobronchial valves seen in the chest radiograph of the same patient

Nitinol coils, in contrast to EBVs, are non-blocking devices that would create the BLVR effect via parenchymal compression from the pre-formed coil shape after deployment, and thereby improve the elastic recoil of lungs and support to the small airway walls. Two RCTs[27,28] reported statistically and clinically significant benefits in lung function, exercise tolerance and respiratory quality of life measure. From such limited data, it appears that coils can be an alternative BLVR option for patients with collateral ventilation in the target lobe(s) and homogenous disease distribution, in whom EBV implantation would not be an effective option. Reported complications of BLVR with coils usually appear in the early weeks after the procedure, and which include COPD exacerbations, chest pain, pneumothorax, pneumonia and haemoptysis. Another BLVR method is the delivery of thermal vapour ablation to the diseased segments, resulting in irreversible parenchymal fibrosis and hence volume reduction. Several small studies had revealed significant improvements in lung function and quality of life after the procedure.[29,30] Limited data on the utilisation of lung sealant (synthetic polymer) to occlude the airways and collateral channels of the target areas via creation of atelectasis, remodelling and scarring had also reported clinical benefits in lung function, dyspnoea and quality of life in patients with advanced emphysema.[31,32] However, both thermal vapour and lung sealant treatment had been associated with the adverse effects related to local acute inflammation, leading to fever, cough, sputum and dyspnoea. Lastly, use of drug-eluted stents to create bypass passages in bronchial airways to deflate air trapped in emphysematous regions had also been described, though no sustainable clinical benefits had been noted in a recent trial.[33]

The 2016 updated GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guidelines for COPD had adopted a relatively conservative stand towards BLVR therapies: "…available evidence is insufficient to determine their benefit-risk ratios, cost-effectiveness and possible roles in the strategy of care for patients with predominant emphysema and … should not be used outside clinical trials until more data are available."[17]

Conclusion

While pulmonary interventions have been emerging as potential non-pharmacological treatment options for obstructive airway diseases, the clinical evidence and experience are still relatively limited at this juncture. Although such interventions can be performed in a minimally invasive manner via flexible bronchoscopy, more data on the risk and benefit with such interventions, together with careful case selections and preparations would be necessary.

References

1. Affonce DA and Lutchen KR. New perspectives on the mechanical basis for airway hyperreactivity and airway hypersensitivity in asthma. J Appl Physiol (1985) 2006; 101(6): 1710-19.
2. James AL, Elliot JG, Jones RL, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. Am J Respir Crit Care Med 2012; 185(10): 1058-64.
3. Danek CJ, Lombard CM, Dungworth DL, et al. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol (1985) 2004; 97(5): 1946-1953.
4. Mayse ML, Laviolette M, Rubin AS, et al. Clinical pearls for bronchial thermoplasty. J Bronchol Interv Pulmonol 2007; 14(2): 115-123.
5. Cox PG, Miller J, Mitzner W, et al. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. Eur Respir J 2004; 24(4): 659-663.
6. Laxmanan B and Hogarth DK. Bronchial thermoplasty in asthma: current perspectives. Journal of asthma and allergy 2015; 8: 39-49.
7. Cox G, Miller JD, McWilliams A, et al. Bronchial thermoplasty for asthma. Am J Respir Crit Care Med 2006; 173(9): 965-969.
8. Cox G, Thomsen NC, Rubin AS, et al. AIR Trial Study Group. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007 ; 356 (13): 1327-1337.
9. Pavord ID, Cox G, Thomson NC, et al. RISA Trial Study Group. Safety and efficacy of bronchial thermoplasty in symptomatic severe asthma. Am J Respir Crit Care Med 2007; 176(12): 1185-91.
10. Castro M, Rubin AS, Laviolette M, et al. AIR2 Trial Study Group. 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(2): 116-124.
11. Thomsen NC, Rubin AS, Niven RM, et al. AIR Trial Study Group. Long-term (5 year) safety of bronchial thermoplasty: asthma intervention research (AIR) trial. BMC Pulm Med 2011; 11:8.
12. Pavord ID, Thomsen NC, Niven RM, et al. Research in Severe Asthma Trial Study Group. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol 2013; 111(5): 402-407.
13. Wechsler ME, Laviolette M, Rubin AS, et al. Asthma Intervention Research 2 Trial Study Group. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol 2013; 132(6): 1295-1302.
14. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (update 2016) Available from: http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/ Accessed 5 July 2016.
15. Laxmanan B, Egressy K, Murgu S, et al. Recent advances in Chest Medicine: Advances in Bronchial Thermoplasty. Chest. 2016 Mar 19. pii: S0012-3692(16)42633-4. doi: 10.1016/j.chest.2016.03.012. [Epub ahead of print]
16. Solway J, Irvin CG. Airway smooth muscle as a target for asthma therapy. N Engl J Med 2007; 356(13): 1367-1369.
17. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2016). Available from: https://www.guidelines.co.uk/gold/copd Accessed 5 July 2016.
18. Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung volume reduction surgery vs. medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006; 82(2): 431-443.
19. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung volume reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003; 348(21): 2059-2073.
20. Marchetti N, Criner GJ. Surgical approaches to treating emphysema: lung volume reduction surgery, bullectomy and lung transplantation. Semin Respir Crit Care Med 2015; 36: 592-608.
21. Herth FJ, Slebos DJ, Rabe KF, et al. Endoscopic lung volume reduction: an expert panel recommendation. Respiration 2016; 91: 241-250.
22. Scuiba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010; 363:1233-44.
23. Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomized controlled trial. Lancet 2015; 386: 1066-73.
24. Herth FJ, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013; 41: 302-308.
25. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med 2015; 373: 2325-35.
26. Gompelmann D, Herth FJ, Slebos DJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration 2014; 87: 485-491.
27. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomized controlled trial. Lancet Respir Med 2013; 1: 233-40.
28. Deslee G, Mal H, Dutau H, et al. Lung volume reduction coil treatment vs. usual care in patients with severe emphysema. The REVOLENS randomized clinical trial. JAMA 2016; 315(2): 175-184.
29. Herth FJ, Valipour A, Shah PL, et al. Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multi-centre, parallel-group,open-label, randomized controlled STEP-UP trial. Lancet Resp Med 2016; 4(3): 183-193.
30. Snell G, Herth FJ, Hopkins P, et al. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. Eur Respir J 2012; 39: 1326-1333.
31. Kramer MR, Refaely Y, Maimon N, et al. Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema. Chest 2012; 142: 1111-1117.
32. Come C, Kramer MR, Dransfield MT, et al. A randomized trial of lung sealant versus medical therapy for advanced emphysema. Eur Respir J 2015; 46(3): 651-662.
33. Shah PL, Cardoso PF, Cwtti E, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomized, sham-controlled, multi-centre trial. Lancet 2011; 378: 997-1005.

Wildebeests, Baobabs and Tanzania

Dr Yu-kai LI
LMCHK

Dr Yu-kai LI

Africa - a continent of mystery to many. To some, it may be just a vast land of desert. It is dry, hot, suffocating and overflows with poverty. Many of us feel nonchalant about Africa, yet the eastern part is where we *Homo Sapiens* supposedly rooted from. For readers that are the Beatles' fans, perhaps LSD(Lucy in the Sky with Diamonds) will ring a bell. Africa occupies more land than triple the size of China, 2/3 in the Northern Hemisphere and 1/3 south. The latitudes of the northern cities are much higher than Hong Kong and even Shanghai, so they get much cooler during the winter seasons as well. In particular, Eastern Africa is a highland around a thousand metres high in altitude, located along the Indian Ocean rim and the Great Rift Valley. Kilimanjaro, the famous snow mountain 5,900 metres high, stands on the plateau. The *Ngorongoro* (pronounced as n-go-ro-n-go-ro) Crater National Park is situated at 2,600m altitude, and was only 6ºC one night when we were there, right adjacent to the Equator.

Before I embarked on my adventure, I had friends asking me about management of heat stroke and Ebola infection etc., however, all these seemed irrelevant once my journey began.

Our safari tour began at the Arusha Kilimanjaro Airport, where we were greeted by our Tanzanian professional travel agent with a safari car and accompanied us to four of their sixteen national parks. These safari cars are specially designed for animal watching. The roofs can be elevated to facilitate passengers to see through the windows or from higher angles. The accommodation was wonderful, with excellent lodge rooms and food service. We were blessed to have Izhark, our driver guide who took care of us throughout our 6 days journey. Izhark was fluent in English, professional and very knowledgeable. We spotted a Bible on his car's dashboard, and I started to wonder how Catholic influence infiltrated Africa. Izhark, not ready to disappoint us on our first encounter, explained that Tanzania was an English colony in the 1880s, and subsequently presented as a gift to England's royal cousin, Germany. After WWI it was administered by the League of Nations, the former international organisation prior to the UN and declared independence as a country in 1964. We truly appreciated Izhark's service and hospitality; in return, I left him my triple sensors watch as a souvenir.

Comparing to its neighbour Kenya, Tanzania has more national parks and they are larger in size. Serengeti, the oldest and largest, spans 15000 square kilometres and is 10 times larger than the *Maasai Mara Park*, its equator neighbour. It is famous for its annual migration of over 1.5 million wildebeests and 250,000 zebras, along with numerous Nile crocodiles and honey badgers. *Seregeti* means an endless plain in the local language. The tour was indeed an over-saturated wildlife feast for all of us.

The "*Big Five*" is the term coined by big-game hunters and refers to the five animals most difficult to hunt on foot. The Big Five consists of lions, elephants, buffaloes, leopards, and rhinoceros. They were chosen for the difficulty involved in hunting and the degree of danger involved, rather than their size. The term was later adopted by safari tour operators for marketing purposes, and is now commonly used among tourists and wildlife guides in the safari.

Despite Izhark's effort, it was a pity our group failed to spot a rhino, which is classified as critically endangered(CE). He informed us there are only 25 rhinos in the Ngorongoro Crater Park , and it is a very rare chance for tourists to see them. In fact, the number of other animals in the *Big Five* is also diminishing; lions and elephants are classified as vulnerable species (VU), while buffaloes and leopards are near threatened (NT). Nonetheless, we were lucky enough to see many of the Big Five, except for any rhino. A stunning and breath-taking moment of our adventure was a scene when

HONG KONG SANATORIUM & HOSPITAL

CURRENT OG PRACTICE 2016

Date **Sunday, 23 October 2016**
Venue **Ballroom, JW Marriott Hotel Hong Kong**

08:30 – 09:00	Registration	
09:00 – 09:10	Welcome	Dr. CHAN Woon Tong, Joseph
Part I		
09:10 – 09:30	Development of IVF in Hong Kong	Prof. HO Pak Chung
09:30 – 09:50	Pre-implantation Genetic Testing	Dr. TANG Oi Shan
09:50 – 10:10	Surgical Management of Subfertility	Dr. Joyce CHAI
10:10 – 10:30	Oocyte Freezing - Putting Motherhood On Hold	Dr. LOK Hung, Ingrid
10:30 – 11:00	**Coffee Break**	
Part II		
11:00 – 11:20	Induction of Labour for Post-date Pregnancies - Earlier or Later?	Dr. LAM Sze Wing, Helena
11:20 – 11:40	Hepatitis B Carriers and Pregnancy: Should We Do More?	Dr. CHEUK Kwan Yiu, Queenie
11:40 – 12:00	The Use of Progesterone for Prevention and Treatment of Threatened or Recurrent Miscarriages	Dr. WAN Hei Lok, Tiffany
12:00 – 12:20	Practice of O&G in the Third World Countries	Dr. LI Kandice
12:20 – 13:30	**Lunch**	
Part III		
13:30 – 13:50	New Development in Uterine Fibroid Management	Dr. YUEN Pong Mo
13:50 – 14:10	Female Urinary Incontinence	Dr. LAU Nga Ting, Winnie
14:10 – 14:30	The Role of Laparoscopic Surgery in Gynaecological Cancer	Dr. TAM Kar Fai
14:30 – 15:00	**Coffee Break**	
Part IV		
15:00 – 15:20	Abnormal NIPT Results – What's Next?	Dr. LEUNG Tse Ngong, Danny
15:20 – 15:40	Should Umbilical Cord Arterial PH be Routinely Measured in Modern Obstetrics?	Dr. CHAN Wan Pang
15:40 – 16:00	Use of Mifegyne (RU486) in Termination of Pregnancy and Management of Miscarriage	Dr. CHAN Woon Tong, Joseph

*Content is subject to change without prior notice

REGISTRATION IS ON A FIRST COME, FIRST SERVED BASIS

Reserve your place at www.hksh.com/og-registration or by phone: 2835 3426

CME Accreditations by Various Colleges (Pending) | CNE Accreditations (Pending)

Registration Deadline: **Friday, 7 October 2016** | **For Medical and Health Professionals Only**

a lioness dashed with a piece of meat in her mouth, still dripping blood and already traced by three of her brothers. Another highlight was when two leopards played on trees on a small hill, and when nature called out of the blue, the two mated efficiently for a very short time, in only three or four seconds, with very loud roaring. They parted only for a brief rest, and would soon return to complete another round of act.

Animals may be endangered, but they could also be dangerous to humans. The most dangerous of them all is the elephant, followed by buffalo, then rhino. During our adventure, a middle-aged elephant stood in front of our car, blocking our way and starring at us with its small angry eyes, reluctant to give way. Aside from my cold sweat, I can only remember our hearts pounding, and am now very glad I can live to share my experience.

Other carnivores were shy in general, and it was common to see coalitions (groups of cheetahs) through the grassland and bushes, actively avoiding our cars. Contrary to what most media portray, lions appeared lazy with their hunting, especially when they feeled full. They were often asleep and could be sighted commonly on the roadside.

On the contrary, the graminivores were always hungry and looking to bite constantly. Besides elephants and buffaloes, other common graminivores are zebras, wildebeests, giraffes and numerous kinds of antelopes including gazelle, impala, topi, waterbuck, springbok and dik-dik. They were so shy yet so energetic, and ran quickly with a beautiful posture. Dik-diks were particularly lovely, very cute with big naive eyes.

Annually, the circular great wildebeest migration begins in *Ngorongoro*, the southern Serengeti in Tanzania. It is nature's way to ensure adequate grazing. It usually lasts from December to May, when the calving season and plenty of rain-ripened grass is available for a quarter million zebras that precedes the 1.7 million wildebeests and the following hundreds of thousands of other plain game, including around half-million gazelles. We were lucky enough to visit in June 2016, and saw an endless queuing of tens of thousands wildebeests marching. The magnificent exodus lasted tens of miles beyond our eyes as we reached over the elevated roof of our safari car.

A Tsetse fly bit me once at my right heel. Yes, it is indeed the kind notoriously associated with the human sleeping sickness or trypanosomiasis, frequently mentioned in our tropical medical textbook; but not Kala-azar, which is caused by sand fly. I decided to ignore it unless something sinister happens, since its probability was not high, and I was not ready to ruin my adventure by fussing over nothing.

Few calves were born before the season, but hardly any survived. The main reason is that very young calves are more noticeable to predators when mixed with older calves from the previous year. As the rains end in May, the animals start moving northwest into the areas around the Grumeti River, where they typically remain until late June. The crossing of the Grumeti and Mara rivers begins in July because crocodiles are lying in wait, and ready to prey. The herds arrive in Kenya in late July and August, where they stay for the remainder of the dry season, except the Thomson's and Grant's gazelles move only east and west. In early November, with the start of the short rains the migration starts moving south again, to the short grass plains of the southeast, usually arriving in December with plenty of time for calving in February.

About 250,000 wildebeests die during the journey from Tanzania to Maasai Mara, southwestern Kenya. Death is usually from thirst, hunger, exhaustion, or predation. Most of them enter nature's food chain.

The Baobab tree is a relative to the cotton tree in Hong Kong. According to a legend, the gods had just finished creating the world, when they realised that they had forgotten to plant the baobab tree. So they hastily threw it down from heaven. Is it a way of asking for forgiveness, that the gods tied its destiny with elephants? *Monkey bread*, the fruit of the Baobab tree, is very rich in vitamins and has two times more calcium than milk. But the baobab seed can only germinate if it has first passed through a pachyderm's stomach. This means that when the elephants disappear, so will the baobabs. If elephants walk on the pathways of Africa, baobabs continue to grow. If gods tied man's destiny with nature, then there is one certainty: they would be as crazy as the movie, *The Gods Must Be Crazy*.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
★HKMA Badminton Tournament 2016 ★HKMAPS 3rd Seasonal Photo Competition 4	5	★HKMA Yau Tsim Mong Community Network – What's New in HIV Medicine, 2016 ★FMSHK Officers' Meeting ★HKMA Council Meeting 6	★HKMA Golf Tournament 2016 7	★HKMA Hong Kong East Community Network – Better LUTS Management, Better Days For Your Patients ★HKMA Kowloon East Community Network - Seminar on Management of Common Breastfeeding Problems: What Primary Care Doctors Need to Know and Practice? ★HKMA Structured CME Programme with HKS&H Session 8: IVF in Current Era 8	9	10
★Refresher Course for Health Care Providers 2016/2017- Handling sexually transmitted diseases 11	12	★Scientific Symposium and Case Discussion - Practical Pearls for Management of Common Dermatologic Cases 13	★Hong Kong Neurosurgical Society Monthly Academic Meeting –An emerging magnet for brain 14	15	16	17
★HKMA Badminton Tournament 2016 18	19	20	21	★FMSHK Executive Committee Meeting 22	★HKMA Yau Tsim Mong Community Network - Update on Prevention of COPD Exacerbations 23	★HKMA Tennis Tournament 2016 24
25	26	27	28	★HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2016 (Session 4): Management of Arrhythmia 29	30	

呼特康®
flutiform®
fluticasone propionate/formoterol

Introducing *flutiform*®:

For rapid and sustained control of asthma, *flutiform*® can be a change for the better.[1-9]

flutiform® combines the well-tolerated and potent anti-inflammatory effects of fluticasone with the fast onset and sustained bronchodilatory action of formoterol.[1-5] Clinical studies show it offers effective, rapid and sustained control of asthma symptoms.[3-7] ***flutiform***® is available in an ergonomic aerosol device that delivers a consistently high fine particle fraction across flow rates in an *in-vitro* study.[8,9]

Flutiform® pressurised inhalation, suspensions - Abridged Product Information

COMPOSITION Fluticasone propionate and formoterol fumarate dihydrate at strengths of 50 µg/5 µg, 125 µg/5 µg or 250 µg/10 µg per actuation. **INDICATIONS** Regular treatment of asthma where the use of a combination product (an inhaled corticosteroid and a long-acting β_2 agonist) is appropriate: For patients not adequately controlled with inhaled corticosteroids and 'as required' inhaled short-acting β_2 agonist; or for patients already adequately controlled on both an inhaled corticosteroid and a long-acting β_2 agonist. ***Flutiform***® 50 µg/5 µg and 125 µg/5 µg inhalers are indicated in adults and adolescents aged 12 years and above. ***Flutiform***® 250 µg/10 µg inhaler is indicated in adults only. **DOSAGE AND ADMINISTRATION** For inhalation use. The patient should be shown how to use the inhaler correctly by a physician or other healthcare professional. Patients should be given the strength of ***Flutiform***® containing the appropriate fluticasone propionate dose for their disease severity (note that ***Flutiform***® 50 µg/5 µg per actuation is not appropriate in patients with severe asthma). The appropriate strength should be taken as two inhalations, twice-daily (normally in the morning and evening) and used every day, even when asymptomatic. ***Flutiform***® should not be used in children under 12 years. Prescribers should be aware that in asthmatics, fluticasone propionate is as effective as some other inhaled steroids when administered at approximately half the total daily microgram dose. Total daily dose can be increased if asthma remains poorly controlled by administering a higher strength inhaler. Appropriate doses of the β_2-agonist and inhaled corticosteroid (ICS) in separate inhalers, or the ICS alone, should be prescribed if a patient requires doses outside the recommended dose regimens. Patients should be assessed regularly and once asthma is controlled, treatment should be reviewed and stepped down to the lowest effective dose, or an ICS alone. It is extremely important to regularly review patients as their treatment is stepped down. ICSs alone are first line treatment for most patients. ***Flutiform***® is not intended for initial treatment of mild asthma. For patients with severe asthma the ICS therapy should be established before prescribing a fixed-dose combination product. Patients on ***Flutiform***® must not use an additional LABA. An inhaled SABA should be taken for immediate relief of asthma symptoms arising between doses. The ***AeroChamber Plus***® spacer device is recommended in patients who find it difficult to use the inhalers; re-titration should always follow the introduction of a spacer device. Patients should be advised to contact their prescriber when the ***Flutiform***® dose indicator is getting near zero. **CONTRAINDICATIONS** Hypersensitivity to any of the active substances or excipients. Pregnancy. Lactation. **PRECAUTIONS** ***Flutiform***® should not be used for the first treatment of asthma, to treat acute asthma symptoms or for prophylaxis of exercise-induced asthma. It should not be initiated during an exacerbation, during significantly worsening or acutely deteriorating asthma, and should not be stopped abruptly. Patients should use their ***Flutiform***® maintenance treatment as prescribed, even when asymptomatic. If a patient experiences serious asthma-related adverse events or exacerbations, they should continue treatment but also seek medical advice. Patients should be reviewed as soon as possible if there is any indication of deteriorating asthma control. In the case of sudden and progressive deterioration, which is potentially life-threatening, an urgent medical assessment should be carried out. Use with caution in patients with: pulmonary tuberculosis; quiescent tuberculosis; fungal, viral or other infections of the airway; thyrotoxicosis; pheochromocytoma; diabetes mellitus (consider additional blood sugar controls); uncorrected hypokalaemia; predisposition to low levels of serum potassium; impaired adrenal function (monitor HPA axis function regularly) ; hypertrophic obstructive cardiomyopathy; idiopathic subvalvular aortic stenosis; severe hypertension; aneurysm or other severe cardiovascular disorders. There is risk of potentially serious hypokalaemia with high doses of β_2-agonists or concomitant treatment with β_2-agonists and drugs that can induce or potentiate a hypokalaemic effect. Particular caution is recommended in unstable or acute severe asthma and other conditions when the likelihood for hypokalemia adverse effects is increased. Monitoring of serum potassium levels is recommended during these circumstances. Formoterol may induce prolongation of the QTc interval. Caution must be observed when treating patients with existing prolongation of QTc interval. ***Flutiform***® should be discontinued immediately if there is evidence of paradoxical bronchospasm. Systemic effects with an ICS may occur, particularly at high doses for prolonged periods or when combined with potent CYP3A4 inhibitors, but are less likely than with oral corticosteroids. Use of a spacer device may also cause an increased systemic exposure. Increased exposure can be expected in patients with severe hepatic impairment. Prolonged treatment with high doses of corticosteroids may result in adrenal suppression and acute adrenal crisis, particularly in adolescents and children or potentially as a result of trauma, surgery, infection or rapid dose reduction. Patients should be advised that ***Flutiform***® contains a small amount of ethanol; however this negligible amount does not pose a risk to patients. ***Flutiform***® is not recommended in children under 12 years of age. **ADVERSE REACTION** Potentially serious side-effects: hyperglycaemia; depression; aggression; behavioural changes (predominantly in children); paradoxical bronchospasm; agitation; vertigo; palpitations; ventricular extrasystoles; angina pectoris; tachycardia; hypertension; dyspnoea; peripheral oedema; Cushings Syndrome; adrenal suppression; growth retardation; cataract and glaucoma; hypersensitivity reactions and QTc interval prolongation. Please refer to the SPC for details of non-serious side-effects and those reported for the individual molecules. **INTERACTIONS** Caution is advised in long-term co-administration with strong CYP3A4 inhibitors (e.g. ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nelfinavir, saquinavir, ketoconazole and telithromycin); co-administration should be avoided if possible. Ritonavir in particular should be avoided, unless the benefits outweigh the risks of systemic side-effects. Caution is advised with use of non-potassium sparing diuretics (e.g. loop or thiazide), xanthine derivatives, glucocorticosteroids, L-Dopa, L-thyroxine, oxytocin, alcohol or other adrenergic drugs. There is an increased risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the risk of arrhythmias in patients being treated with digitalis glycosides. Concomitant use of β-adrenergic drugs can have a potentially additive effect. Extreme caution should be taken when using formoterol fumarate with drugs known to prolong the QTc interval, such as tricyclic antidepressants or MAOIs (and for two weeks following their discontinuation), as well as antipsychotics (including phenothiazines), quinidine, disopyramide, procainamide and antihistamines. Concomitant use of an MAOI or a similar agent, such as furazolidone or procarbazine, may precipitate hypertensive reactions. β-blockers and formoterol fumarate may inhibit the effect of each other. β-blockers may produce severe bronchospasm in asthma patients, and they should not normally be treated with β-blockers including those that are used as eye drops to treat glaucoma. Under certain circumstances, e.g. as prophylaxis after myocardial infarction, cardioselective β-blockers could be considered with caution. **PRESENTATION** Pressurised inhalation suspension, in a pressurised metered dose inhaler (pMDI), containing fluticasone propionate and formoterol fumarate dihydrate at strengths of 50 µg/5 µg, 125 µg/5 µg or 250 µg/10 µg per actuation.
Full prescribing information is available upon request. HK-FLU-0251-V1-0615

References: 1. ***flutiform***® Approved Summary of Product Characteristics (20/06/13). **2.** Price D, Bousquet J. Real-world perceptions of inhaled corticosteroid/long-acting β_2-agonist combinations in the treatment of asthma. *Resp Med* 2012; 106 (S1): S4-S8. **3.** Thomas M, Haughney J, Price D. Physicians' attitudes towards combination therapy with inhaled corticosteroids and long-acting β_2-agonists: an observational study in UK specialist care. *Prag Obs Res* 2011; 2: 25-31. **4.** Aalbers R *et al.* Onset of bronchodilation with fluticasone/formoterol combination versus fluticasone/salmeterol in an open-label, randomized study. *Adv Ther* 2012. Published online 17 October 2012 (www.advancesintherapy.com). **5.** Bodzenta-Lukaszyk A *et al.* Fluticasone/formoterol combination therapy is at least as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulm Med* 2011; 11: 28-37. **6.** Tamm M *et al.* Inhaled corticosteroid and long-acting β_2-agonist pharmacological profiles: effective asthma therapy in practice. *Resp Med* 2012; 106 (S1): S9-S19. **7.** Mansur AH, Kaiser K. Long-term safety and efficacy of fluticasone/formoterol combination therapy in asthma. *J Aerosol Med Pulm Drug Deliv* 2012; 25 (0): 1-10. **8.** Newman SP, Chan HK. In Vitro/In Vivo Comparisons in Pulmonary Drug Delivery. *J Aerosol Med Pulm Drug Deliv* 2008; 21 (1): 77-84. **9.** Johal B, Howald M, Fischer M, Marshall J. Venthoye G. Fine particle profile of fluticasone propionate/formoterol fumarate versus other combination products: the DIFFUSE Study. *Comb Prod Ther* DOI 10.1007/S13556-013-0003-9

For detailed information, please refer to full prescribing information.

Mundipharma (Hong Kong) Ltd
Units 801B-802A, 8/F, Tower B, Manulife Financial Centre,
223-231 Wai Yip Street, Kwun Tong, Kowloon
Tel: 852 3929 4666 Fax: 852 3929 4668

mundipharma

HK-FLU-0268-V2-0816

Certificate Course For Nurses And Allied Health Professionals | CME/CNE Course | Course No. C287

Certificate Course on
Respiratory Medicine 2016

Jointly organised by

The Federation of Medical Societies of Hong Kong
香港醫學組織聯會

Hong Kong Thoracic Society
香港胸肺學會

CHEST Delegation Hong Kong and Macau

Objectives:

To enhance the understanding of common respiratory diseases. To provide recent update and practical tips in Respiratory Medicine.

Date	Topics	Speakers
5 Oct	Recent advance in Interventional Bronchology	Dr. Wong King Ying Associate Consultant, WTSH
12 Oct	New drug, new hope – New era of pharmacotherapy for COPD	Dr. Tam Cheuk Yin Consultant, TMH
19 Oct	Pleural diseases – air, fluid and bugs in the pleura	Dr. Cheung Pik Shan Associate Consultant, UCH
26 Oct	Antimicrobial resistance in respiratory tract infections – management and control strategies	Dr. Lee Man Po Consultant, QEH
2 Nov	(I) Trouble Shooting of CPAP therapy for Obstructive Sleep Apnoea (II) Telemonitoring for Home Mechanical Ventilation	Miss Lit Pik Kee, Maggie Respiratory APN, QEH
9 Nov	Clinical application of radiological imaging in respiratory disease and interpretation of lung function tests	Dr. Lam Wai Kei Associate Consultant, NDH

Date : 5 October 2016 - 9 November 2016 (Every Wednesday)
Time : 7:00 p.m. – 8:30 p.m.
Venue : Lecture Hall, 4/F., Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong
Language Media : Cantonese (Supplemented with English)
Course Fee : HK$750 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax: 2865 0345 Email: info@fmshk.org

CME / CNE / CPD Accreditation in application
Application form can be downloaded from website: http://www.fmshk.org

Date / Time	Function	Enquiry / Remarks
4 SUN 1:00 PM	**HKMA Badminton Tournament 2016** Organiser: The Hong Kong Medical Association;Venue: MMRC	Miss Denise KWOK Tel: 2527 8285
2:00 PM	**HKMAPS 3rd Seasonal Photo Competition** Organiser: The Hong Kong Medical Association; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Miss Heiman CHAN Tel: 2527 8285
6 TUE 1:00 PM	**HKMA Yau Tsim Mong Community Network – What's New in HIV Medicine, 2016** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHENG Kai Chi; Speaker: Dr. TSANG Kay Yan; Venue: Jade Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
8:00 PM	**FMSHK Officers' Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Gallop, 2/F, Hong Kong Jockey Club Club House, Shan Kwong Road, Happy Valley, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
9:00 PM	**HKMA Council Meeting** Organiser: The Hong Kong Medical Association; Chairman: Dr. CHOI Kin; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Christine WONG Tel: 2527 8285
7 WED 11:30 AM	**HKMA Golf Tournament 2016** Organiser: The Hong Kong Medical Association; Venue: Hong Kong Golf Club	Mr. Ian KWA Tel: 2527 8285
8 THU 1:00 PM	**HKMA Hong Kong East Community Network – Better LUTS Management, Better Days For Your Patients** Organiser: HKMA Hong Kong East Community Network; Chairman: Dr. TUET On Sang; Speaker: Dr. LEE Chan Wing, Francis; Venue: HKMA Wanchai Premises, 5/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Hong Kong	Ms. Candice TONG Tel: 2527 8285 1 CME Point
1:00 PM	**HKMA Kowloon East Community Network - Seminar on Management of Common Breastfeeding Problems: What Primary Care Doctors Need to Know and Practice?** Organiser: HKMA Kowloon East Community Network and Primary Care Office of the Department of Health; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. FUNG Wai Han, Amy; Venue: Lei Garden Restaurant (利苑酒家), Shop no. L5-8, apm, Kwun Tong, No. 418 Kwun Tong Road, Kwun Tong, Kowloon	Miss Hana YEUNG Tel: 2527 8285 1 CME Point
2:00 PM	**HKMA Structured CME Programme with HKS&H Session 8: IVF in Current Era** Organiser: The Hong Kong Medical Association & Hong Kong Sanatorium & Hospital; Speaker: Dr. Lok Hung, Ingrid; Venue: Function Room A, HKMA Dr. Li Shu Pui Professional Education Centre, 2/F, Chinese Club Building, 21-22 Connaught Road Central, Hong Kong	HKMA CME Dept. Tel: 2527 8452 1 CME Point
11 SUN 2:15 PM	**Refresher Course for Health Care Providers 2016/2017-** **Handling sexually transmitted diseases** Organiser: Hong Kong Medical Association, HK College of Family Physicians HA-Our Lady of Maryknoll Hospital; Speaker: Dr. Kwan Chi Keung; Venue: Training Room II, 1/F, OPD Block, Our Lady of Maryknoll Hospital, 118 Shatin Pass Road, Wong Tai Sin, Kowloon	Ms. Clara TSANG Tel: 2354 2440 2 CME Points
13 TUE 1:00 PM	**Scientific Symposium and Case Discussion - Practical Pearls for Management of Common Dermatologic Cases** Organiser: Hong Kong Medical Association; Speaker: Dr. Sheila C. Chua; Venue: Cordis Hotel, Mongkok	Mr. LAI Tel: 3954 5301 1.5 CME Points
14 WED 7:30AM	**Hong Kong Neurosurgical Society Monthly Academic Meeting –** **An emerging magnet for brain** Organiser: Hong Kong Neurosurgical Society; Speaker: Dr HO Man Kit, Jason; Chairman: Dr CHAN Yung; Venue: Seminar Room, G/F, Block A, Queen Elizabeth Hospital	Dr. LEE Wing Yan, Michael Tel: 2595 6456 Fax.: 2965 4061 1.5 CME Points
18 SUN 1:00 PM	**HKMA Badminton Tournament 2016** Organiser: The Hong Kong Medical Association; Venue: MMRC	Miss Denise KWOK Tel: 2527 8285
22 THU 8:00PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windor Social Service Building, 15 Hennessy Road, Wanchai, Hong Kong	Ms. Nancy CHAN Tel: 2527 8898
23 FRI 1:00 PM	**HKMA Yau Tsim Mong Community Network - Update on Prevention of COPD Exacerbations** Organiser: HKMA Yau Tsim Mong Community Network; Chairman: Dr. CHAN Ka Wing, Joseph; Speaker: Dr. TSE Hoi Nam; Venue: Pearl Ballroom, Level 2, Eaton, Hong Kong, 380 Nathan Road, Kowloon	Ms. Candice TONG Tel: 2527 8285 1 CME Point
24 SAT 7:30 PM	**HKMA Tennis Tournament 2016** Organiser: The Hong Kong Medical Association; Venue: Kowloon Tong Club	Miss Denise KWOK Tel: 2527 8285
29 THU 1:00 PM	**HKMA KECN, HKCFP & UCH - Certificate Course for GPs 2016 (Session 4): Management of Arrhythmia** Organiser: The Hong Kong Medical Association; Venue: Kowloon Tong ClubOrganiser: HKMA Kowloon East Community Network & Hong Kong College of Family Physicians & United Christian Hospital; Chairman: Dr. AU Ka Kui, Gary; Speaker: Dr. YUE Chiu Sun, Sunny; Venue: Conference Room, G/F, Block K,United Christian Hospital (UCH), 130 Hip Wo Street, Kwun Tong, Kowloon	Ms. Polly TAI / Ms. Cordy WONG Tel: 3949 3430 (Ms. TAI) / 3949 3087 (Ms. WONG) 1 CME Point

Upcoming Meeting

8-9/10/2016	**The 9th Hong Kong Allergy Convention - Novel Strategies for Prevention and Treatment of Allergic Disorders** Organiser: Hong Kong Institute of Allergy; Venue: Hong Kong Convention and Exhibition Centre	HKAC 2016 Secretariat Tel: 2559 9973
23/10/2016 8:30am-4:00pm	**Current OG Practice 2016** Organisers: Hong Kong Sanatorium & Hospital; Venue: Ballroom, JW Marriott Hotel Hong Kong, Pacific Place, 88 Queensway, Admiralty	Tel: 2835 3426 ogsymposium2016@hksh.com www.hksh.com/og-registration
12-13/11/2016 8:30am-10:00pm	**24th Annual Scientific Meeting of Hong Kong College of Radiologists** Organiser: Hong Kong College of Radiologists; Venue: Hong Kong Academy of Medicine Jockey Club Building, 99 Wong Chuk Hang Road, Aberdeen, HKSAR, China	Tel: 2871 8787 Fax: 2871 8898 Email: hkcr@hkam.org.hk

Answers to Dermatological Quiz

Answer:

1. The clinical differential diagnoses include cutaneous lymphoma, lymphocytoma cutis, Jessner lymphocytic infiltrate, lupus erythematosis tumidus, granulomatous rosacea and the plaque form of polymorphous light eruptions.

2. Skin biopsy is essential to establish the diagnosis. Often, further sophisticated investigations like immunohistochemical staining for T-cell/B-cell or T-cell receptor/Immunoglobulin gene rearrangement study are necessary to further classify the cutaneous lymphoid diseases.

   The biopsy in this patient showed reactive lymphoid hyperplasia, with polyclonal B-cell predominant and a "top heavy" lymphocytic infiltration in the dermis (versus a "bottom heavy" infiltration in lymphoma). Thus the picture is compatible with a clinical diagnosis of lymphocytoma cutis.

   However, lymphocytoma cutis is not a specific disease entity. It is considered as a form of benign reactive lymphoid hyperplasia. Follow-up and a repeated biopsy at the right site is often necessary to establish its benign nature, as it tends to mimic the B cell lymphomas.

3. Cutaneous lymphoma is still the most important diagnosis that must be excluded. Before that it should not be regarded as reactive lymphoid hyperplasia, which is also known as cutaneous pseudolymphoma. The nomenclature and classification are confusing among both the clinicians and pathologists. Reactive lymphoid hyperplasia (Cutaneous pseudolymphoma) is not a specific disease, but just an inflammatory reaction to known or unknown stimuli, resulting in an accumulation of benign lymphocytic inflammatory cells. Different histological patterns include B-cell predominate picture (e.g. lymphocytoma cutis), T-cell predominate picture (e.g. Jessner lymphocytic infiltrate, lupus erythematosis tumidus) and mixed B and T-cell (drug induced hypersensitivity reaction, Lyme's disease).

   Most cases of pseudolymphoma are idiopathic. The reported causes include drugs (anticonvulsants, typically phenytoin and carbamazepine), infections (*Borrelia burdoferri, Helicobacter pylori*), arthropod bites (insect and spider), tattoo, jewellery, vaccination, etc.

Dr Lai-yin CHONG
MBBS(HK), FRCP(Lond, Edin, Glasg), FHKCP, FHKAM(Med)
Specialist in Dermatology & Venereology

RELVAR™ ELLIPTA™

(fluticasone furoate and vilanterol inhalation powder)

Practical efficacy

First and Only Once-Daily ICS/LABA combination for **Asthma** patients uncontrolled on ICS and 'as-needed' SABA across Hong Kong & Macau[1,2]

- Delivering **24 hours of continuous, sustained efficacy**[3,4]
- Administered in a simple, **Once-Daily dosage** regimen[3]
- Delivered in **ELLIPTA™ - an easy to use inhaler device** with majority of patients able to use it correctly at first time [5*]
- **Well accepted safety and tolerability profile**[3,4]

* Pooled data from three 12-24 weeks randomized, double-blind studies in which OD Relvar Ellipta 100/25 or OD Fluticasone Furoate 100 mcg was delivered via the Ellipta dry powder inhaler (DPI) (n=989)[5]

Relvar Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:
• patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists[1].

Dosage strengths indicated for treatment of Asthma:

Relvar Ellipta 200/25
micrograms
One inhalation, once-daily[1]

Relvar Ellipta 100/25
micrograms
One inhalation, once-daily[1]

Notes to Prescriber

- Patients should not stop therapy with Relvar in asthma, without physician supervision.
- Relvar should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required.

Abbreviated Prescription Information **NAME OF THE PRODUCT** RELVAR™ ELLIPTA™ **QUALITATIVE AND QUANTITIVATIVE COMPOSITION** Pre-dispensed dose of 100 mcg or 200mcg of fluticasone furoate and 25 mcg vilanterol (as trifenatate). Inhalation powder. **INDICATIONS** ***Asthma*** **Relvar Ellipta 100/25mcg & 200/25mg** is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate: · patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists. ***COPD*** **(Chronic Obstructive Pulmonary Disease) Relvar Ellipta 100/25mcg** is indicated for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy. **DOSAGE AND ADMINISTRATION** ***Asthma*** **Adults and adolescents aged 12 years and over** One inhalation of **Relvar Ellipta 100/25mcg or 200/25mg** once daily. Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. A starting dose of **Relvar Ellipta 100/25mcg** should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting $beta_2$-agonist. If patients are inadequately controlled on **Relvar Ellipta 100/25mcg**, the dose can be increased to Relvar Ellipta 200/25mcg, which may provide additional improvement in asthma control. The maximum recommended dose is **Relvar Ellipta 200/25mcg** once daily. **Children aged under 12 years** The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the indication for asthma. ***COPD*** **Adults aged 18 years and over** One inhalation of **Relvar Ellipta 100/25mcg** once daily. **Relvar Ellipta 200/25mcg** is not indicated for patients with COPD. **Paediatric population** There is no relevant use of Relvar Ellipta in the paediatric population in the indication for COPD. Patients usually experience an improvement in lung function within 16-17 minutes of inhaling Relvar Ellipta. **Elderly patients (>65 years) & renal impairment** No dose adjustment. Relvar Ellipta is for inhalation use only. After inhalation, the patient should rinse their mouth with water without swallowing. Patients should be made aware that Relvar Ellipta must be used regularly, even when asymptomatic. Patients should be regularly reassessed by a healthcare professional so that the strength of **Relvar Ellipta** they are receiving remains optimal and is only changed on medical advice. **CONTRAINDICATIONS** Hypersensitivity to the active substances or to any of the excipients **WARNINGS AND PRECAUTIONS** *Deterioration of disease* Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician. Patients should not stop therapy with fluticasone furoate/vilanterol in asthma or COPD, without physician supervision since symptoms may recur after discontinuation. Asthma-related adverse events and exacerbations may occur during treatment with fluticasone furoate/vilanterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of 1 treatment with Relvar Ellipta. *Paradoxical bronchospasm Paradoxical bronchospasm* may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Relvar Ellipta should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary. *Cardiovascular effects* such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease. *Systemic corticosteroid effects* Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. *Pneumonia* in patients with COPD An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal. 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 receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m2 and patients with a (forced expiratory volume) FEV_1<50% predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs. The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking Relvar Ellipta 200/25mcg was numerically higher compared with those receiving Relvar Ellipta 100/25mcg or placebo. No risk factors were identified. **INTERACTIONS** *Interaction with beta-blockers $beta_2$-adrenergic blockers* may weaken or antagonise the effect of $beta_2$-adrenergic agonists. Concurrent use of both non-selective and selective $beta_2$-adrenergic blockers should be avoided unless there are compelling reasons for their use. *Interaction with CYP3A4 inhibitors* Caution is advised when co-administering with strong CYP 3A4 inhibitors as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, and concomitant use should be avoided. **PREGNANCY AND LACTATION** Pregnancy Administration of fluticasone furoate/vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. Breast-feeding A decision must be made whether to discontinue breast-feeding or to discontinue fluticasone furoate/vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. **ADVERSE REACTIONS** Pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, headache, extrasystoles, nasopharyngitis, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, fractures, pyrexia. **OVERDOSE** There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. Abbreviated Prescribing Information based on Relvar Ellipta Summary of Product Characteristics, Hong Kong (Sep 2014).

References: 1. IMS Health pharmaceutical data 2010-2015. Assessed on 26 May 2015. **2.** Prescribing Information of therapeutics agents indicated for asthma treatment, MIMS Drug Reference (Concise Prescribing Information) Hong Kong. Issue 1, 2015 **3.** Relvar (Fluticasone Furoate and vilanterol inhalation powder) Hong Kong Prescribing Information, 2014. **4.** Bleecker ER et al. Fluticasone furoate-vilanterol 100/25 mcg compared with fl uticasone furoate 100 mcg in asthma: a randomized trial. JACI In Practice. 2014;2(5):553-561. **5.** Svedsater H et al. Ease of use of a two-strip dry powder inhaler (DPI) to deliver fluticasone furoate/vilanterol (FF/VI) and FF alone in asthma. BMC Pulmonary Medicine 2013, 13:72.

The material is for the reference and use by healthcare professionals only. For adverse event reporting, please call GlaxoSmithKline Limited at (852) 9046 2498 (Hong Kong) or (853) 6366 7071 (Macau).
Full Prescribing Information is available upon request. Please read the full prescribing information prior to administration, available from GlaxoSmithKline Limited.

gsk

GlaxoSmithKline Limited
23 / F, Tower 6, The Gateway, 9 Canton Road, Tsimshatsui, Kowloon, Hong Kong.
Tel: (852) 3189 8989 Fax: (852) 3189 8931 www.gsk.com.hk

GlaxoSmithKline Limited - Macau Branch
Avenida Infante D. Henrique, No.43-53A, Edf. Macau Square 21 andar C, Macau.
Tel: (853) 2871 5569 Fax: (853) 2871 5987

Theravance

HKRX/FFT/0010/15 (07/2017)

Vannair™ pMDI
budesonide/formoterol

AstraZeneca
阿 斯 利 康

Help your COPD patients do more

COPD

Vannair pMDI (budesonide/formoterol)

- significantly improves lung function in 5 minutes[1,2]
- shows faster onset of bronchodilation than salmeterol/fluticasone[1]
- makes a significant improvement in breathing[2]
- effectively prolongs time to exacerbation[2]
- eases bronchoconstriction and controls inflammation[3]