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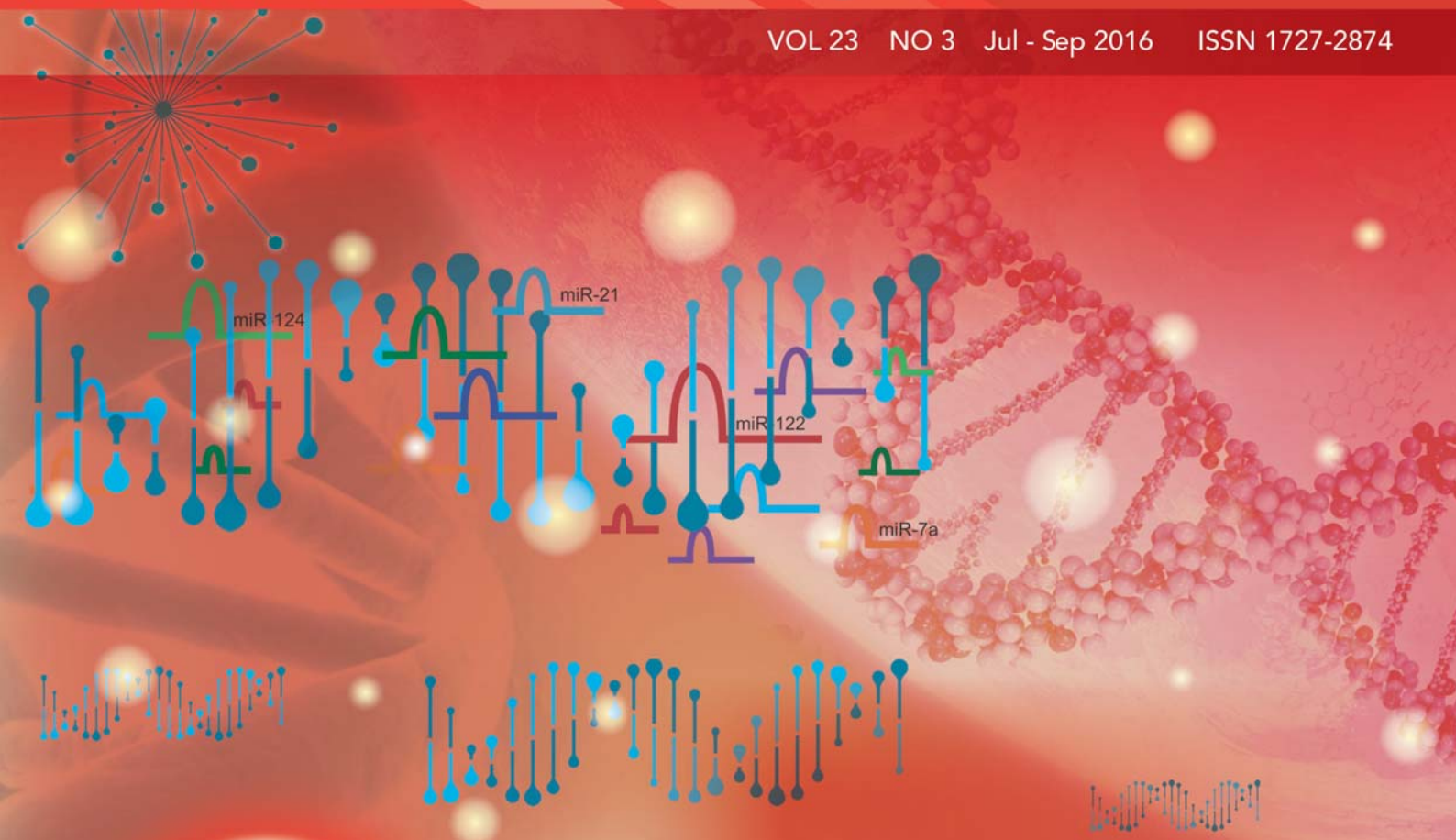

The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

From the Changing Role of Pharmacists to the Age of Biologics

It was reported in the news in July and August 2016 that many new pharmacy graduates this year were not hired by the Hospital Authority and had difficulty in finding a job in the community pharmacies. These graduates were not as lucky as the pharmacy graduates in the previous years. Starting in 2010, due to the abundance of visitors from mainland China to purchase consumer products and drugs, many pharmacies were open in Hong Kong. During this period, the salary of community pharmacists increased as there was insufficient number of pharmacists to fill the vacancies available. Naturally, all the new pharmacy graduates were taken up by the Hospital Authority. In 2009, there was only 30 pharmacy graduates each year from the CUHK. The HKU started the Pharmacy Degree course in 2009 with 25 graduates in 2012. Since then, CUHK increased the intake of pharmacy students. In 7 years, the number of pharmacy graduates increase from 30 to 87 per year. Since 2014, there is slow down in the economy in China and less visitors from China, quite a few community pharmacies closed down. This year, the HA and private hospitals employ about 50 pharmacists. More and more pharmacy graduates seek employment in multinational pharmaceutical companies and local manufacturers. Instead of dispensing and counselling of patients, they are taking up roles in regulatory affairs, clinical trials, product information in the multinational pharmaceutical companies to production of drugs, quality assurance and quality control in a GMP manufacturer. It has always been difficult for government to predict the manpower of healthcare professionals such as doctors, nurses and pharmacists. It is not advisable to drastically cut the number of students for the Pharmacy Program in both universities because the need may change with government policy and changes in economic situation. According to the recommendation by WHO, the ratio of pharmacist to population should be 2000:1. In Hong Kong, the ratio is only 3800:1, we actually do not have enough pharmacists to provide the adequate pharmaceutical service to patients in Hong Kong. There are a lot of areas in which pharmacists are underutilized, such as in community pharmacies and elderly care in Old Age Homes. The professional societies should unite and influence the government to put in more resources for the benefit of patients in Hong Kong. The manpower need and the work force situation need to be reviewed annually.

In 2014, the U.S. Food and Drug Administration (FDA) approved 9 new drugs and biologics in the treatment of cancer and added 10 notable new indications or formulations to existing drug labels. In 2015, the FDA approved another 13 new drugs for cancer. The development of new therapeutic biologics, in particular, is a trend that continues to drive cancer drug development and approval by the FDA. The FDA's acceleration of the review process for cancer drug approval is another important factor because treatment options are limited for many cancer patients with advanced disease. In this issue, the review of 14 newly registered Oncology Drugs in Hong Kong in 2015 is incorporated. These include ceritinib, afatinib, ipilimumab, nivolumab, pembrolizumab, dabrafenib, vismodegib, enzalutamide, ibrutinib, idelalisib, binutuzumab, brentuximab, pomalidomide and trastuzumab emtansine. These drugs covers five types of cancers including non-small cell lung cancer (NSCLC), skin cancer, prostate cancer, blood cancer and breast cancer. Based on the understanding of pathogenesis of cancer, various signalling pathways and the molecules that confer proliferation advantage in cancer have been identified. Targeted therapy poses an important dimension of cancer treatment due to the specificity to cancer cells and more favorable side effects profile over conventional chemotherapy. The indication, dosage, common side effects, proposed mechanism of action, related clinical studies and clinical benefits over existing agents of each new drug are discussed in the article on "Review of Newly Registered Oncology Drugs in Hong Kong" on Page 86.

According to the World Health Organisation, there are more than 350 million people of all ages that suffer from depression and it is the leading cause of disability worldwide which is a major contributor to the global burden of disease. Mild depression can affect a person's daily activities whereas severe depression may lead to suicide attempts. Major depressive disorder (MDD) is a challenging clinical condition where only about 30-40% of patients achieve full remission with first-line therapy of adequate duration. About one-third of patients do not achieve remission even after therapy with as many as four different antidepressant medications. To make matters worse, many of antidepressants are associated with side effects that limit their tolerability and reduce their compliance. In the article of "Considering Cognitive Function Treatment in Major Depressive Disorder on Page 98, Sarah Kong wrote about the pharmacological and non-pharmacological therapies available to treat patients with major depressive disorder. More recently, it has been noted that cognitive function plays a major role in major depressive disorder and that a novel serotonin reuptake inhibitor, vortioxetine has been shown to improve cognitive functioning.

Chronic kidney diseases (CKD) can lead to various complications and conditions, one of them being long-term electrolyte imbalance. This condition causes hyperplasia in the parathyroid gland, and would result in decline in response to drug therapies. In order to maintain the efficacy of drug therapies, pharmacist-led medication therapy management clinic (MTMC) was implemented. On page 80, WOO, Yuk Hei Alex; LEE Chui Ping; SO, Wai Yin Simon and LAI, Wah Kit Kandy wrote that provision of pharmacist care and MTM service should be on a regular and continuous basis for the best outcomes of SHPT management.

In the article on page 111, LEE, Kin Ho; WANG, Fang; HUANG, Ye-Qing; CHEUNG, Hon-Yeung wrote about the "Chemical Constituents and Bioactivities of Rhododendri Daurici Folium". It is a herbal medicine with a long history for treating chronic and acute tracheitis and asthma. This herb is composed of a wide range of bioactive components providing useful biological effects but very few studies have reported on the relations between the bioactivities and therapeutic effect. To authenticate Rhododendron dauricum L., HPLC analysis would be conducted as well as morphological identification.

To close off, I would like to remind you that the Hong Kong Pharmacy Conference is on 18-19 February 2017 at the Hong Kong Convention and Exhibition Centre. There are many exciting programs available. Please check at the website: www.pharmacyconference.org for registration and information.

Cheng Mary Catherine
Managing Editor
15 November 2016

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

Prepared by Annie Tsoi, William Kwan, Hercules Tse, Bryan Kan, Kelvin Cheng

Sulfonylurea Users with Renal Impairment in Higher Hypoglycaemic Risk Than Metformin Users

Date: July 13, 2016

Hypoglycaemia is a significant side effect of sulfonylureas. Gliclazide is regarded as a first choice sulfonylurea for type 2 diabetic patient in many countries to lower the risk of hypoglycaemia. However, data is insufficient to support this recommendation for patients especially those with impaired renal function. Therefore, a study has been conducted to determine the association between the use of sulfonylureas and risk of hypoglycaemia in relation to renal function and sulfonylurea metabolic group compared with use of metformin.

The aforementioned study is a singled-blinded population-based cohort study analysing data from patients using the Clinical Practice Research Datalink (CPRD) database in England from 2004 to 2012. The study has included 120,803 new users aged 18 or above who had had non-insulin antidiabetic agent prescribed at least once. Associations between sulfonylurea dose, renal impairment, type of sulfonylurea used, and risk of hypoglycaemia, were determined using Cox proportional hazard models. Adjustments were made for possible confounding variables like age, sex, comorbidity and drug use.

The study showed that the risk of hypoglycaemia in sulfonylurea user with an estimated glomerular filtration rate of less than 30 mL/min/1.73 m^2 is significantly higher than metformin user. (4.96, 3.76 to 6.55) High sulfonylurea dose is associated with higher risk of hypoglycaemia. (3.12, 2.68 to 3.62) Gliclazide, the recommended sulfonylurea, showed similar risk of hypoglycaemia compared with other sulfonylureas.

The study concluded that the use of sulfonylurea by patient with renal impairment was associated with higher hypoglycaemic risk than the use of metformin. The risk is significant regardless of the activity of the sulfonylurea metabolite. Gliclazide is not superior to other sulfonylureas in this aspect.

Source: www.bmj.com

Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs

Date: July 14, 2016

Ventricular tachycardia can result from a myocardial infarction episode which leads cardiac cell death and abnormality in the cardiac conduction system. Patients with recurrent ventricular tachycardia despite of anti-arrhythmic drug therapy can opt for catheter ablation or dose increase for the anti-arrhythmic drug. A randomized-controlled trial was done to compare the two treatment options.

A total of 259 post-myocardial infarction patients with implantable cardioverter defibrillator (ICD) and at least one episode of ventricular tachycardia during treatment with a class I or III anti-arrhythmic drug were included in the study. They were randomized into the ablation group or escalated-therapy group. For patients in the escalated therapy group, amiodarone was initiated if it was not taken previously. Patients receiving amiodarone with a dose less than 300mg daily had their dose increased. Mexiletine 200mg three times daily was added for patients receiving an amiodarone dose higher than 300mg daily. Catheter ablation was done for patients in the ablation group within 14 days of randomization. The primary outcome of the study was a composite of death, three or more ventricular tachycardia episodes within 24 hours, or an appropriate ICD shock after 30 days of treatment.

The primary outcome occurrence rate was significantly lower in the ablation group, with a hazard ratio of 0.72 (95% confidence interval: 0.53-0.98, p=0.04). The statistical significance was even higher if only patients treated with amiodarone at baseline were included, where the hazard ratio for the ablation group was 0.55 (95% CI: 0.38-0.8, p=0.001). No statistical significant differences were found in those not treated with amiodarone at baseline.
This study showed that patients with recurring ventricular tachycardia despite of anti-arrhythmic drug therapy can benefit more from catheter ablation than a dose increase, especially for those patients who had already been taking amiodarone.

Source: www.nejm.org

Pioglitazone Use and Risk of Bladder Cancer in Patients with Type 2 Diabetes: Retrospective Cohort Study Using Datasets from Four European Countries

Date: August 16, 2016

Pioglitazone is an antidiabetic drug of the thiazolidinediones class. It is used to treat type 2 diabetes mellitus, yet an increased risk of bladder cancer development is suspected. Although some pharmacoepidemiology studies suggest an increased bladder cancer incident in patients taking pioglitazone, it is argued that these studies were not free from selection bias. Pioglitazone was normally used a second line or third line agents on patients with poorer glycaemic control, so the subjects themselves may have a higher risk of bladder cancer development irrespective of the antidiabetic agent used.

A retrospective cohort study using European subjects was done to determine whether pioglitazone does increase bladder cancer risk. Using healthcare databases from the Netherlands,

Finland, Sweden and the UK, 56,337 patient cases who had exposed to pioglitazone had been identified. Each exposed patient was matched with one nearest non-exposed patient (nearest match cohort) and at most 10 non-exposed patients (multiple match cohort) in the database according to variables such as duration of treated diabetes and number of previous diabetes treatment. The later matching gives 317,109 control subjects.

The hazard ratios of bladder cancer of patients exposed to pioglitazone versus control were 0.99 (95% confidence interval 0.75-1.30) and 1.00 (0.83-1.21) for nearest match and multiple match cohort respectively. The hazard ratios for patients with more than 48 months of pioglitazone exposure were 0.86 (0.44-1.66) and 1.12 (0.63-2.01), while that of those taken a cumulative pioglitazone dose of more than 40,000 mg had hazard ratios of 0.65 (0.33-1.26) and 0.81 (0.44-1.47). It was shown that patients taking pioglitazone were not at a higher risk of developing bladder cancer.

In this study, long term use of pioglitazone was not found to increase the risk of bladder cancer. These findings were also similar to several other large-scale studies with multiple years of follow-up.

Source: www.bmj.com

Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma

Date: September 1, 2016

Long-acting beta-agonists (LABAs) have been shown to increase the risk of asthma-related death among adults and the risk of asthma-related hospitalization among children. It is unknown whether the concomitant use of inhaled glucocorticoids with LABAs mitigates those risks. This trial prospectively evaluated the safety of the LABA salmeterol, added to fluticasone propionate, in a fixed-dose combination in children.

Children 4 to 11 years of age who required daily asthma medications and had a history of asthma exacerbations in the previous year were assigned randomly to receive fluticasone propionate plus salmeterol or fluticasone alone for 26 weeks. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization), as assessed in a time-to-event analysis.

Among the 6208 patients, 27 patients in the fluticasone–salmeterol group and 21 in the fluticasone-alone group had a serious asthma-related event (all were hospitalizations); the hazard ratio with fluticasone–salmeterol versus fluticasone alone was 1.28 (95% confidence interval [CI], 0.73 to 2.27), which showed the noninferiority of fluticasone–salmeterol (P=0.006). A total of 265 patients (8.5%) in the fluticasone–salmeterol group and 309 (10.0%) in the fluticasone-alone group had a severe asthma exacerbation (hazard ratio, 0.86; 95% CI, 0.73 to 1.01).

In this trial involving children with asthma, salmeterol in a fixed-dose combination with fluticasone was associated with the risk of a serious asthma-related event that was similar to the risk with fluticasone alone.

Source: www.nejm.com

Interpretation of the Evidence for the Efficacy and Safety of Statin Therapy

Date: September 8, 2016

The article explains how the evidence that is available from randomised controlled trials yields reliable information about the efficacy and safety of statin therapy. In addition, it discusses how claims that statins commonly cause adverse effects reflect a failure to recognise the limitations of other sources of evidence about the effects of treatment.

Evidence from randomised trials shows that statin therapy reduces the risk of major vascular events by about one-quarter for *each* mmol/L reduction in LDL cholesterol during *each* year (after the first) that it continues to be taken. The absolute benefits of statin therapy depend on an individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved. Statin therapy has been shown to reduce vascular disease risk during each year it continues to be taken, so larger absolute benefits would accrue with more prolonged therapy, and these benefits persist long term.

The only serious adverse events that have been shown to be caused by long-term statin therapy are myopathy, new-onset diabetes mellitus, and, probably, haemorrhagic stroke. Typically, treatment of 10 000 patients for 5 years with an effective regimen (eg, atorvastatin 40 mg daily) would cause about 5 cases of myopathy, 50–100 new cases of diabetes, and 5–10 haemorrhagic strokes. However, the benefit-risk ratios for these cases are mostly positive. The study showed that statin therapy can lead to adverse events (e.g. muscle pain or weakness) in up to 0.5–1·0% of patients. However, placebo-controlled randomised trials have shown definitively that almost all of the symptomatic adverse events related to statin therapy in routine practice are not actually caused by it, it is usually a represent misattribution.

Source: www.thelancet.com

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Date: September 18, 2016

Romosozumab is a monoclonal antibody that binds sclerostin, to increases bone formation and decreases bone resorption. The study enrolled 7180 postmenopausal women who had a T score of –2.5 to –3.5 at the total hip or femoral neck. Patients

were randomly assigned romosozumab injections (dose: 210 mg) or placebo monthly for 12 months. Afterwards, patients in each group received denosumab for 12 months, at a dose of 60 mg, administered subcutaneously every 6 months. The coprimary end points were the cumulative incidences of new vertebral fractures at 12 months and 24 months. Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) and nonvertebral fractures.

At 12 months, new vertebral fractures had occurred in 16 of 3321 patients (0.5%), representing a 73% lower risk with romosozumab. Clinical fractures had occurred in 58 of 3589 patients (1.6%) in the romosozumab group, 36% lower risk with romosozumab. Nonvertebral fractures had occurred in 56 of 3589 patients (1.6%) in the romosozumab group and in 75 of 3591 (2.1%) in the placebo group (P=0.10). At 24 months, the rates of vertebral fractures were significantly lower in the romosozumab group than in the placebo group after each group made the transition to denosumab. Adverse events, including instances of hyperostosis, cardiovascular events, osteoarthritis, and cancer, appeared to be balanced between the groups. One atypical femoral fracture and two cases of osteonecrosis of the jaw were observed in the romosozumab group.

For postmenopausal women with osteoporosis, romosozumab was associated with a lower risk of vertebral fracture than placebo at 12 months and, after the transition to denosumab, at 24 months. The lower risk of clinical fracture that was seen with romosozumab was evident at 1 year.

Source: www.nejm.org

Fluticasone Furoate–Vilanterol Reduces Rate of Exacerbations for COPD Patients

Date: September 19, 2016

Guidelines on the management of chronic obstructive pulmonary disease (COPD) are based on studies that may not be directly relevant to clinical purpose. Therefore, the Salford Lung Study was entitled to carry out trials in alternative settings. It has conducted a study to evaluate the effectiveness and safety of the once-daily inhaled combination of fluticasone furoate and vilanterol as compared with existing maintenance therapy.

The randomized controlled investigation trial was carried out in 75 general practices in UK from 2012 to 2014. 2,799 COPD patients aged 40 or above with at least one COPD exacerbations in the previous 3 years were included. They were randomly and evenly assigned to the fluticasone furoate-vilanterol group (once-daily inhaled combination of fluticasone furoate 100 µg and vilanterol 25 µg) or to usual-care group.

The rate of moderate or severe exacerbations among patients with exacerbation within 1 year beforehand was the primary outcome. Secondary outcomes were the rates of primary care contact and secondary care contact, modification of the initial treatment, and the rate of exacerbations among patients with history of exacerbation within 3 years before the trial.

The rate of moderate or severe exacerbations was significantly lower (8.4%, 95% CI: 1.1 to 15.2), with fluticasone furoate–vilanterol therapy than with usual care (P = 0.02). The annual rates of COPD-related contacts to primary or secondary care were similar for the two groups. There were no excess serious adverse events in particular pneumonia in the fluticasone furoate–vilanterol group.

In COPD patients with history of exacerbations, the once-daily inhaled combination of fluticasone furoate and vilanterol was associated with lower rate of exacerbations than usual care, with similar risk of serious adverse events.

Source: www.nejm.org

Is Reduced Antibiotic Prescription for Self-limiting Respiratory Tract Infections in Primary Care Safe?

Date: September 24, 2016

There has been growing concern about the unnecessary use of antibiotics and its consequent antimicrobial resistance and increasing difficulty for treatment. As a result, more research has focused the primary care which includes frontline ambulatory care. In particular, about 60% of the antibiotics prescribed are for respiratory tract infections (RTIs). Therefore, a study has been conducted to determine whether the incidence of pneumonia, peritonsillar abscess, mastoiditis, empyema, meningitis, intracranial abscess, and Lemierre's syndrome is higher in general practices that prescribe fewer antibiotics for self-limiting RTIs.

Cohort study has been chosen as the design of the study and the setting is 610 UK general practices from the UK Clinical Practice Research Datalink. Participants were registered patients with 45.5 million person years of follow-up from 2005 to 2014. The research outcome was measured based on the incidence of aforementioned respiratory illnesses, age group, sex, region, deprivation fifth, RTI consultation rate and general practice.

The study results show a 3% decrease in the proportion of RTI consultations, where Mastoiditis, empyema, meningitis, intracranial abscess, and Lemierre's syndrome were similar in frequency at low prescribing and high prescribing practices, showing no particular increase in new episodes. On the other hand, there might be more cases of peritonsillar abscess and pneumonia each decade. Overall speaking, only a slight increase in the incidence of pneumonia and peritonsillar abscess is expected.

In conclusion, a substantial reduction in antibiotic prescribing was predicted to be associated with only a small increase in numbers of cases observed overall, but specific cautions are required in subgroups more susceptible to pneumonia.

Source: www.bmj.com

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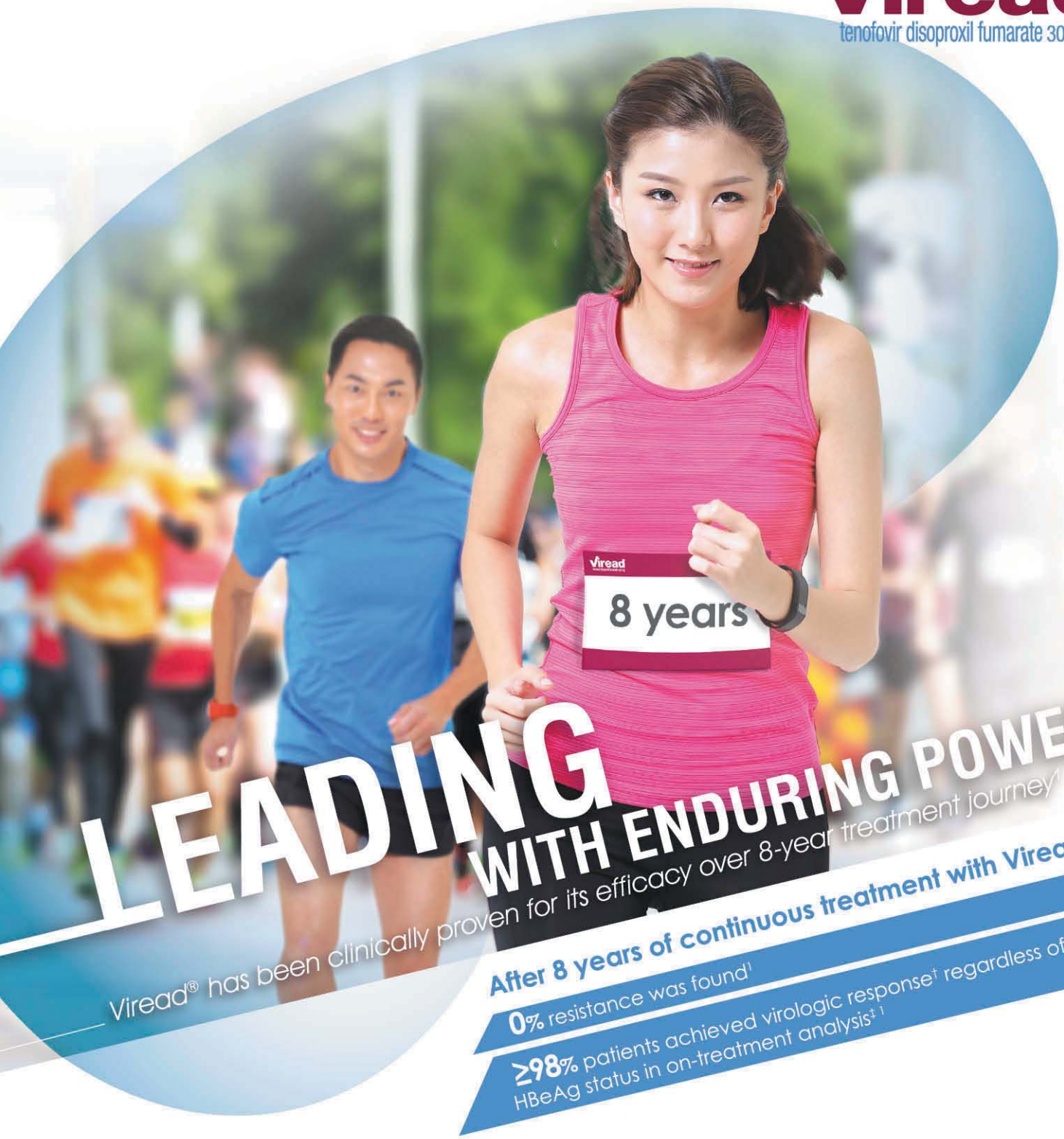

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*By intent-to-treat analysis, virologic response of HBeAg- patients (n=375) and HBeAg+ patients (n=266) are 75% and 58% respectively at week 384. Total 14 hepatocellular carcinomas were found during the study period. The incidence rate of serious drug-related adverse events was 1.2% (n=7) among patients (n=585) who entered the open-label phases.[1]

† HBV DNA <69 IU/mL

‡ Missing=excluded/addition of emtricitabine included

CHB=chronic hepatitis B; HBeAg=hepatitis B e-antigen; HBV=hepatitis B virus

Reference: 1. Marcellin P, Gane E, Flisiak R, et al. Long Term Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B Infection is Safe and Well Tolerated and Associated with Durable Virologic Response with no Detectable Resistance 8 Year Results from Two Phase 3 Trials (OR-229). The Liver Meeting 2014: American Association for the Study of Liver Diseases (AASLD); 2014 November 7-11, 2014; Boston, MA, USA.

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7/28/2016

Retrospective Evaluation of Post-clinic Effect of Pharmacist-led Medication Therapy Management Clinic (MTMC) on Secondary Hyperparathyroidism (SHPT) Management in Patients with End-Stage Renal Disease (ESRD)

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ABSTRACT

Chronic kidney diseases (CKD) can lead to various complications and conditions, one of them being long-term electrolyte imbalance. This condition causes hyperplasia in the parathyroid gland, and would result in decline in response to drug therapies. In order to maintain the efficacy of drug therapies, pharmacist-led medication therapy management clinic (MTMC) was implemented. In a previous 8-month trial, it was proven that pharmacists could improve the patients' control of secondary hyperparathyroidism (SHPT). After the study was over, some of the patients who received MTMC service were no longer enrolled in the service. This study is a 12-month retrospective evaluation to investigate whether MTMC has sustained effect on the control of SHPT parameters after cessation of regular MTMC sessions in these patients. The results showed that percentage of patients achieving the target Ca × P product in the intervention group at 7-12 months was significantly higher than that of the control group (n=59, 88% vs. n=47, 73%; p=0.029). Furthermore, median serum iPTH level of the control group was significantly higher at 1-12 months compared to baseline (27.30 pmol/L, IQR 14.08-39.75 pmol/L vs. 34.30 pmol/L, IQR 19.45-52.18 pmol/L; p=0.017) whereas that of the intervention group did not show significant difference. The study indicated that MTMC has sustained effect on serum iPTH and Ca × P product only but not all parameters, and MTMC should be implemented on a regular basis for SHPT management.

Keywords: *chronic kidney disease; end stage renal disease; secondary hyperparathyroidism; medication therapy management clinic; pharmacist clinic; serum calcium; serum phosphorus; serum intact parathyroid hormone*

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is one of the complications of chronic kidney disease (CKD). It may lead to renal osteodystrophy and other conditions such as vascular and soft tissue calcification. Under chronic stimulation by the electrolyte imbalance, the parathyroid gland may develop into a state of hyperplasia that the patient's response to drug therapy would decline progressively.1 Hence, it is important to manage SHPT promptly and properly.

In 2010, a study entitled "The Impact of Pharmacist-Managed Medication Therapy Management Clinic (MTMC) on the Management of Secondary Hyperparathyroidism in Chronic Kidney Disease Patients" was conducted which was the first randomized control trial (RCT) in Hong Kong to investigate the effect of pharmacist-managed SHPT therapy in patients with end stage renal disease (ESRD) who are on continuous ambulatory peritoneal dialysis (CAPD). At 0, 4 and 8 months, patients in the intervention group were first evaluated by a clinical pharmacist in MTMC sessions just before clinical assessment by renal physicians. The study showed that MTMC improved control of patients' serum calcium (Ca), and maintained a steady control of serum phosphorus (P), calcium-phosphorus product (Ca × P product) and serum intact parathyroid hormone (iPTH) over an 8-month intervention period.[2] After the 8-month study was over, some patients who originally received MTMC service in the intervention group were no longer enrolled in MTMC service due to various operational and logistics reasons. In such patients, it would be meaningful to investigate whether there is a sustained effect on clinical outcomes after regular MTMC follow-ups ceased.

OBJECTIVES

This is a 12-month retrospective evaluation of a previous 8-month prospective randomized controlled trial to evaluate and compare the sustained effect of pharmacist intervention provided by Pharmacist-led MTMC with control group on clinical outcome of SHPT (serum Ca, serum P, Ca × P product and serum iPTH) in patients with ESRD who are on CAPD therapy.

METHODS

All patients enrolled in the previous randomized controlled trial entitled "The Impact of Pharmacist-Managed Medication Therapy Management Clinic (MTMC) on the Management of Secondary Hyperparathyroidism in Chronic Kidney Disease

Patients" (conducted from January to December 2010, in Alice Ho Miu Ling Nethersole Hospital, Hong Kong SAR, China) were recruited into this study.

Primary outcomes include mean serum Ca and P levels at baseline, 1-6 months (Data Period 1) and 7-12 months (Data Period 2). Ca × P product is calculated in this study because a Ca × P product > 4.44 mmol^2/L^2 is associated with increased risk of vascular and soft tissue calcification.[3] Median serum iPTH levels at baseline and at 1-12 months are also measured as primary outcome. **Figure 1** illustrates the study timeline.

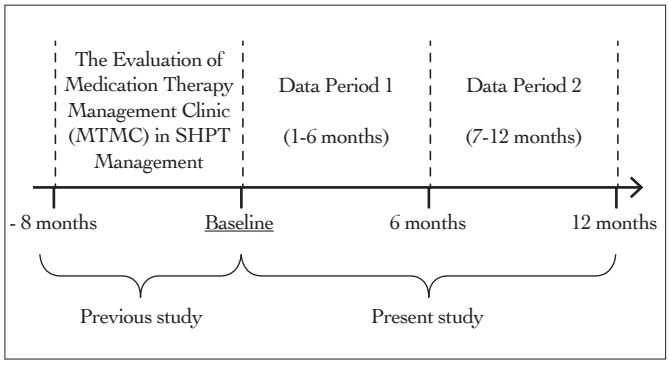

Figure 1. Study Timeline

Secondary outcomes include percentages of patients whose mean serum Ca, P and Ca × P product (at baseline and mean values at Data Period 1 and Data Period 2) and median serum iPTH (at baseline and median values at 1-12 months) were within the categories below as per the Kidney Disease Outcomes Quality Initiative (K/DOQI) or Kidney Disease: Improving Global Outcomes (KDIGO) targets for bone metabolism and disease in CKD:[3-5]

i. Serum Ca concentration
   % of patients between 2.10 – 2.37 mmol/L
   % of patients < 2.10 mmol/L or > 2.37 mmol/L
ii. Serum P concentration
   % of patients between 1.13 – 1.78 mmol/L
   % of patients < 1.13 mmol/L or > 1.78 mmol/L
iii. Ca x P product
   % of patients > 4.44 mmol^2/L^2
   % of patients ≤ 4.44 mmol^2/L^2
iv. Serum iPTH concentration
   % of patients between 2 – 9 × Upper limit of normal (ULN)
   % of patients < 2 × ULN or > 9 × ULN

For intra-group comparison, paired t-test was used to compare between the mean values of serum Ca, serum P and Ca × P product at baseline, Data Period 1 and Data Period 2. Wilcoxon signed-rank test was used to compare the median serum iPTH between baseline and 1-12 months. For between-group comparisons, Independent t-test was used to compare parametric variables while Mann-Whitney U-test was used to compare non-parametric variables. A confidence interval at 95% would be shown. Chi-square test was used for comparison of categorical variables between the intervention and control groups while McNemar test wavs used for with-in group comparison between baseline, Data Period 1 and Data Period 2. Student's t-test was used for baseline comparison of continuous variables that were normally distributed between the two groups.Confidence interval (CI) is set at a level of 95%. Statistical significance is set at 0.05 (2-sided).

RESULTS & DISCUSSION

A total of 133 patients (n=68 and n=65 for intervention and control groups respectively) were enrolled in our study. **Figure 2** shows the flow diagram of study. Baseline characteristics including age, gender and comorbidities did not show significant difference between the two groups **(refer to Table 1)**.

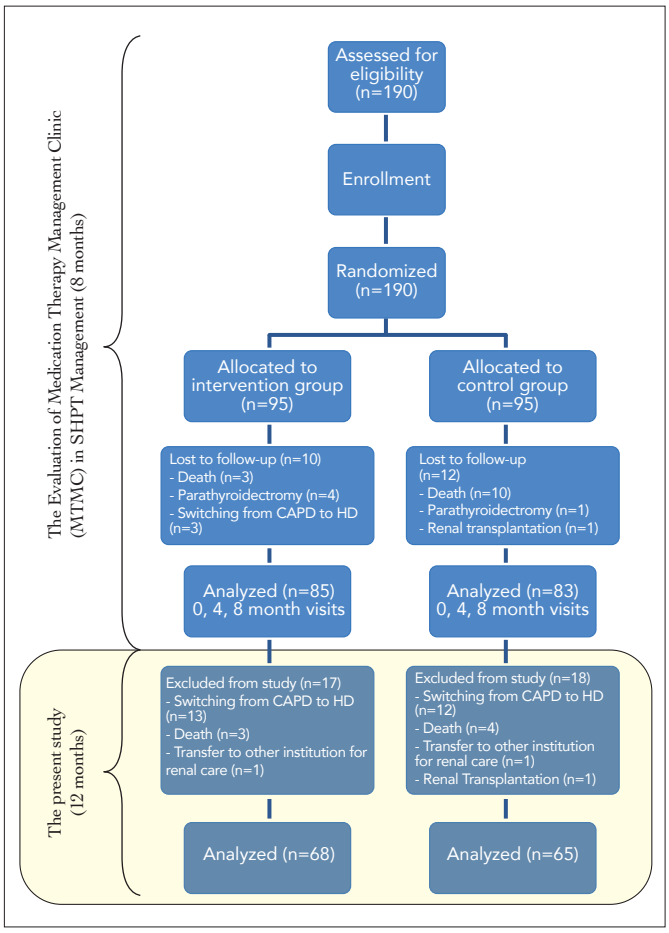

Figure 2. Flow Diagram of Study

Table 1. Baseline Characteristics

Demographics	Overall n = 133	Intervention n = 68	Control n = 65	p-value*
Male sex — n (%)	80 (60)	39 (57)	41 (64)	0.375‡
Age — Mean ± SD	60.8±11.1	58.8±10.1	63.0±11.8	0.054†
Months on CAPD — Mean ± SD	28.8±16.2	26.5±16.7	31.3±15.4	0.870†
Comorbidities				
Hypertension — n (%)	115 (86)	57 (83)	58 (91)	0.177‡
Diabetes Mellitus — n (%)	74 (56)	40 (58)	34 (53)	0.574‡
Dyslipidemia — n (%)	37 (28)	21 (30)	16 (25)	0.485‡
Proteinuria — n (%)	21 (16)	13 (19)	8 (13)	0.316‡
Glomerulonephritis — n (%)	25 (19)	13 (19)	12 (19)	0.989‡

* p value (Intervention group vs. Control group)
† Student's t-test was used.
‡ Chi-square test was used.
CI of all tests were set at 95%.

Serum Ca level

The means in both groups did not show significant difference at baseline (p=0.893), at 1-6 months (p=0.104) and at 7-12 months (p=0.825), as illustrated in **Table 2** and **Figure 3**. A non-significant decreasing trend of mean serum Ca level was

observed in intervention group whereas control group showed a fluctuating pattern. Percentage of patients achieving the K/DOQI target was increasing consistently in the intervention group. However, this growing proportion did not achieve statistical significance when compared with baseline (n=37, 55% vs. n=31, 45%; p=0.210). In the previous local study, the MTMC was found to cause significant improvement on serum Ca level in a consistent manner. Therefore, these findings suggest that the beneficial effect of MTMC on serum Ca level proven in the previous study does not sustain in patients after MTMC stops.

Table 2. Serum Ca

	Overall n = 133	Intervention n = 68	Control n = 65	p-value[a]
Baseline				
Mean — mmol/L ± SD	2.338±0.157	2.345±0.161	2.330±0.153	0.893[b]
No. of patient with level between 2.10-2.37mmol/L — n (%)	68 (51)	31 (45)	37 (58)	0.137[c]
1-6 months (Data Period 1)				
Mean — mmol/L ± SD	2.325±0.141	2.337±0.149	2.313±0.133	0.104[b]
No. of patient with level between 2.10-2.37mmol/L — n (%)	79 (59)	35 (51)[d]	44 (69)[e]	0.034[c]
7-12 months (Data Period 2)				
Mean — mmol/L ± SD	2.325±0.141	2.329±0.139	2.320±0.144	0.825[b]
No. of patient with level between 2.10-2.37mmol/L — n (%)	73 (56)	37 (55)[f]	36 (56)[g]	0.906[c]

[a] p value (Intervention group vs. Control group)
[b] Student's t-test was used.
[c] Chi-square test was used.
[d] p=0.503 (Data Period 1 vs. baseline; by McNemar test)
[e] p=0.189 (Data Period 1 vs. baseline; by McNemar test)
[f] p=0.607 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.210 (Data Period 2 vs. baseline; by McNemar test)
[g] p=0.115 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.999 (Data Period 2 vs. baseline; by McNemar test)
CI of all tests were set at 95%.

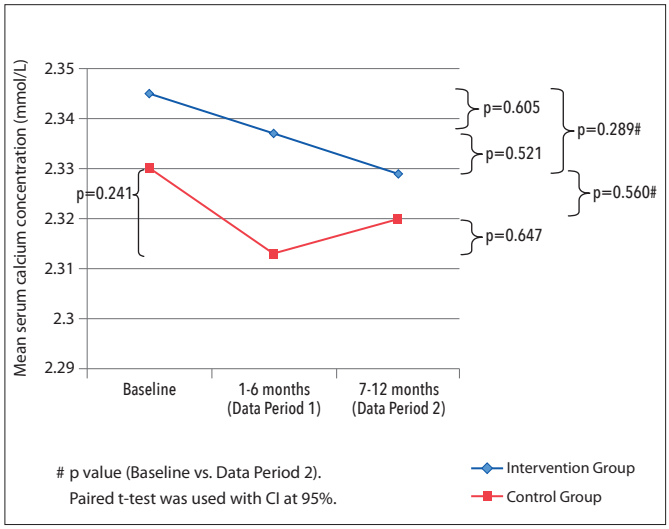

Figure 3. Mean Serum Ca Concentrations at Different Intervals

Serum P level

The means in both groups did not show significant difference at baseline (p=0.421), and at 1-6 months (p=0.952), as shown in **Table 3** and **Figure 4**. Mean serum P was significantly lower in intervention group than control group at 7-12 months (1.562±0.320 mmol/L vs. 1.603±0.431 mmol/L; p=0.026). In the intervention group, the mean serum P at Data Period 1 were significantly higher than that at baseline (1.648±0.402 mmol/L vs. 1.542±0.470 mmol/L; p=0.011) whereas the mean serum P at Data Period 2 became significantly lower than that at Data Period 1 (1.562±0.320 mmol/L vs. 1.648±0.402 mmol/L; p=0.034). A "first increase, later decrease" pattern was observed in both groups. In the previous local study, such pattern was identified in the control group only, while a consistent but non-significant decline of serum P level was observed in the intervention group. This pattern may be related to seasonal and/or dietary changes. Although the proportion of patient in the intervention group with serum P in recommended range was significantly larger than that in the control group in Data Period 2 (n=47, 70% vs. n=33, 52%; p=0.029), this significant finding may be a result of "close-to-significant" difference in proportion at baseline between the two groups. These findings reveal that the MTMC does not have a delayed effect on the control of consistent serum P level.

Table 3. Serum P

	Overall n = 133	Intervention n = 68	Control n = 65	p-value[a]
Baseline				
Mean — mmol/L ± SD	1.578±0.484	1.542±0.470	1.616±0.501	0.421[b]
No. of patient with level between 1.13-1.78mmol/L — n (%)	76 (57)	45 (65)	31 (48)	0.051[c]
1-6 months (Data Period 1)				
Mean — mmol/L ± SD	1.659±0.413	1.648±0.402	1.670±0.427	0.952[b]
No. of patient with level between 1.13-1.78mmol/L — n (%)	76 (57)	39 (57)[d]	37 (58)[e]	0.881[c]
7-12 months (Data Period 2)				
Mean — mmol/L ± SD	1.582±0.377	1.562±0.320	1.603±0.431	0.026[b]
No. of patient with level between 1.13-1.78mmol/L — n (%)	80 (61)	47 (70)[f]	33 (52)[g]	0.029[c]

[a] p value (Intervention group vs. Control group)
[b] Student's t-test was used.
[c] Chi-square test was used.
[d] p=0.238 (Data Period 1 vs. baseline; by McNemar test)
[e] p=0.307 (Data Period 1 vs. baseline; by McNemar test)
[f] p=0.064 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.557 (Data Period 2 vs. baseline; by McNemar test)
[g] p=0.541 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.851 (Data Period 2 vs. baseline; by McNemar test)
CI of all tests were set at 95%.

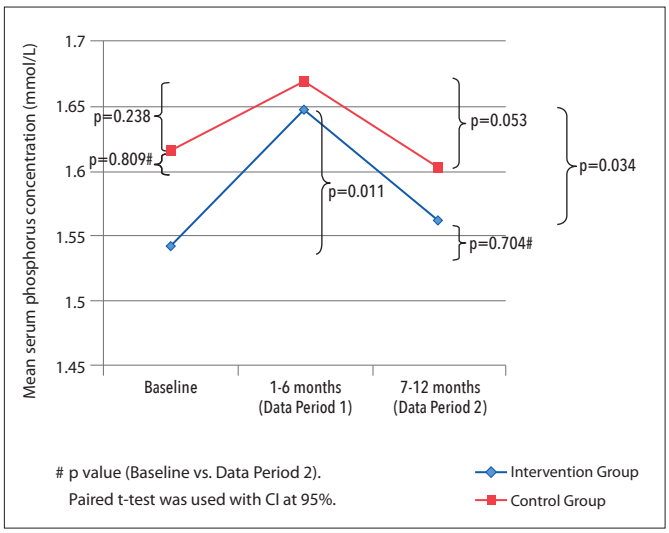

Figure 4. Mean Serum P concentrations at Different Intervals

Ca × P product

The mean Ca × P product in the intervention group was lower than that in the control group at baseline, Data Periods 1 and Data Period 2, as shown in **Table 4** and **Figure 5**; However, only the difference at 7-12 months reached statistical significant (3.646±0.792 mmol²/L² vs. 3.714±1.020 mmol²/L²; p=0.031). "First increase, later decrease" patterns were also observed in both groups and they were very similar to those of serum P. These patterns are consistent with the previous local study that the Ca × P product and serum P level shared similar patterns. The percentage of patients achieving the target Ca × P product in the intervention group at Data Period 2 was significantly higher than that of the control group (n=59, 88% vs. n=47, 73%; p=0.029). Moreover, it was noted that the proportion in the intervention group reached its highest at Data Period 2. Therefore, these findings show that MTMC may have a delayed effect on the percentage of patients who achieved therapeutic goal of Ca × P product. The generally larger proportion of patients at goal of Ca x P product was observed in the intervention group than control group, probably because the MTMC participants acquired more knowledge of renal care through the pharmacist-led MTMC sessions, so that they were more compliant with dietary restriction and were more aware of drug compliance and their health status.

Serum iPTH level

The median serum iPTH in both groups did not show significant difference at baseline (p=0.483), and at 1-12 months (p=0.311), as shown in **Table 5** and **Figure 6**. The intervention group showed a non-significant decreasing trend of median serum iPTH from baseline to data period of 1-12 months (32.00 pmol/L, IQR 14.45-56.30 pmol/L vs. 29.20 pmol/L, IQR 13.35-50.20 pmol/L; p=0.627). On the contrary, the median serum iPTH in control group increased significantly from baseline to data period of 1-12 months (27.30pmol/L, IQR 14.08-39.75 pmol/L vs. 34.30 pmol/L, IQR 19.45-52.18 pmol/L; p=0.017). Although the median serum iPTH at 1-12 months was numerically lower in the intervention group than control group, they did not achieve significant difference between the two groups. These findings point out that the MTMC exerted sustained effect to prevent significant increase in serum iPTH level at 1-12 months after cessation of MTMC follow-ups, slowing down progression of SHPT. These findings are consistent with the previous study which the median serum iPTH level in the intervention group did not show significant changes whereas that in the control group showed a significant increase at 8 months when compared with baseline. The better control of serum iPTH over time in the intervention group may be related to more appropriate selection of drug therapy and pharmacist's effort in rectifying drug related problems. On the contrary, with no pharmacist input in the control group, the decline in response to drug therapy resulted in further parathyroid hyperplasia and the response to therapy would become diminished, leading to progressive increase in serum iPTH level.

CONCLUSION

This study demonstrates that MTMC is able to maintain a stable control of serum iPTH. More importantly, it demonstrates

Table 4. Ca × P product

	Overall n = 133	Intervention n = 68	Control n = 65	p-value[a]
Baseline				
Mean — mmol²/L² ± SD	3.687±1.159	3.625±1.161	3.755±1.161	0.970[b]
No. of patient with level not more than 4.44mmol²/L² — n (%)	103 (77)	55 (80)	48 (75)	0.516[c]
1-6 months (Data Period 1)				
Mean — mmol²/L² ± SD	3.859±1.020	3.855±1.012	3.863±1.037	0.695[b]
No. of patient with level not more than 4.44mmol²/L² — n (%)	97 (73)	50 (72)[d]	47 (73)[e]	0.900[c]
7-12 months (Data Period 2)				
Mean — mmol²/L² ± SD	3.682±0.908	3.646±0.792	3.714±1.020	0.031[b]
No. of patient with level not more than 4.44mmol²/L² — n (%)	106 (81)	59 (88)[f]	47 (73)[g]	0.029[c]

[a] p value (Intervention group vs. Control group)
[b] Student's t-test was used.
[c] Chi-square test was used.
[d] p=0.227 (Data Period 1 vs. baseline; by McNemar test)
[e] p=0.999 (Data Period 1 vs. baseline; by McNemar test)
[f] p=0.013 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.180 (Data Period 2 vs. baseline; by McNemar test)
[g] p=0.999 (Data Period 2 vs. Data Period 1; by McNemar test) and p=0.999 (Data Period 2 vs. baseline; by McNemar test)
CI of all tests were set at 95%.

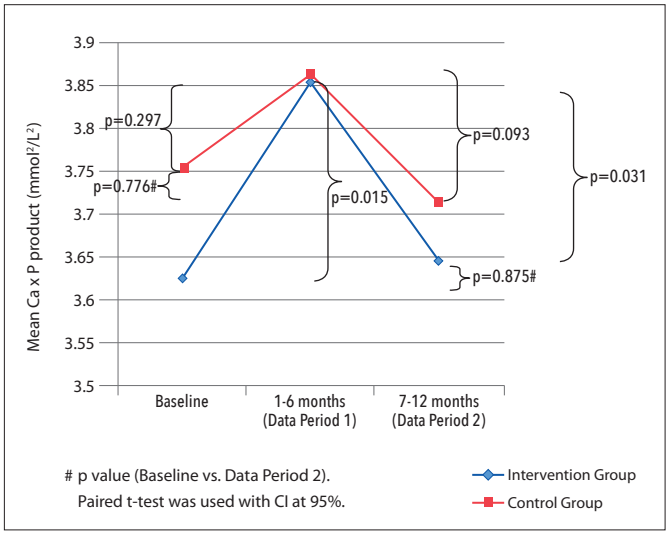

Figure 5. Mean Ca × P Product at Different Intervals

Table 5. Serum iPTH

	Overall n = 133	Intervention n = 68	Control n = 65	p-value[a]
Baseline				
Median — pmol/L (IQR)	28.70 (14.60-47.80)	32.00 (14.45-56.30)	27.30 (14.08-39.75)	0.483[b]
No. of patient with level between 2-9 times ULN — n (%)	89 (67)	44 (65)	45 (70)	0.632[c]
1-12 months				
Median — pmol/L (IQR)	33.10 (17.00-51.80)	29.20d (13.35-50.20)	34.30[e] (19.45-52.18)	0.311[b]
No. of patient with level between 2-9 times ULN — n (%)	93 (70)	43 (64)[f]	50 (76)[g]	0.140[c]

[a] p value (Intervention group vs. Control group)
[b] Mann-Whitney U test was used.
[c] Chi-square test was used.
[d] p=0.627 (1-12 months vs. Baseline; by Wilcoxon signed rank test)
[e] p=0.017 (1-12 months vs. Baseline; by Wilcoxon signed rank test)
[f] p=0.999 (1-12 months vs. Baseline; by McNemar test)
[g] p=0.453 (1-12 months vs. Baseline; by McNemar test)
CI of all tests were set at 95%.

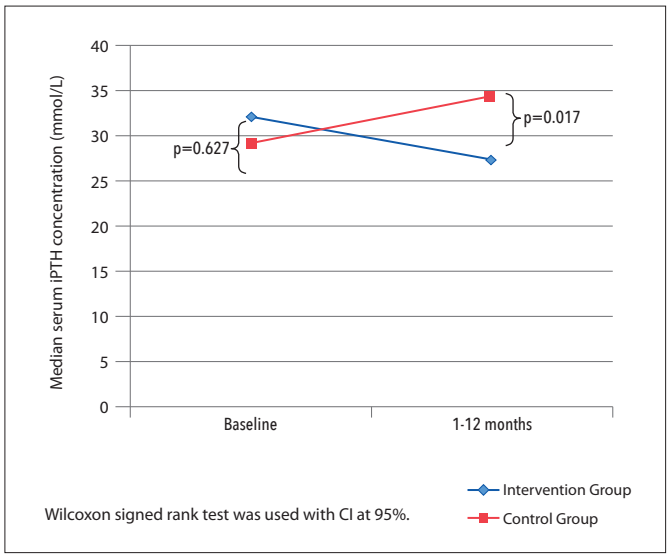

Figure 6. Median Serum iPTH Concentrations at Different Intervals

a sustained effect to prevent significant increase in serum iPTH, slowing down SHPT progression. Besides, MTMC improves the control of Ca × P product at a later stage, leading to significantly lower Ca × P product. Although there were no significant findings for percentage at goal and control of serum Ca concentration, a non-significant decreasing trend of serum Ca level was observed in participants of MTMC. These results revealed that pharmacists are capable of enhancing treatment outcomes (i.e. serum iPTH and percentage of patient at goal of Ca × P product) even certain time after last MTMC follow-up. However, the MTMC is not able to sustain its benefits on serum Ca and P levels once regular MTMC is stopped. This implies that the provision of pharmacist care and MTM service should be on a regular and continuous basis for the best outcomes of SHPT management. The findings would definitely guide the development of clinical pharmacy service in CKD management and provide insights to improvement of the existing clinical service.

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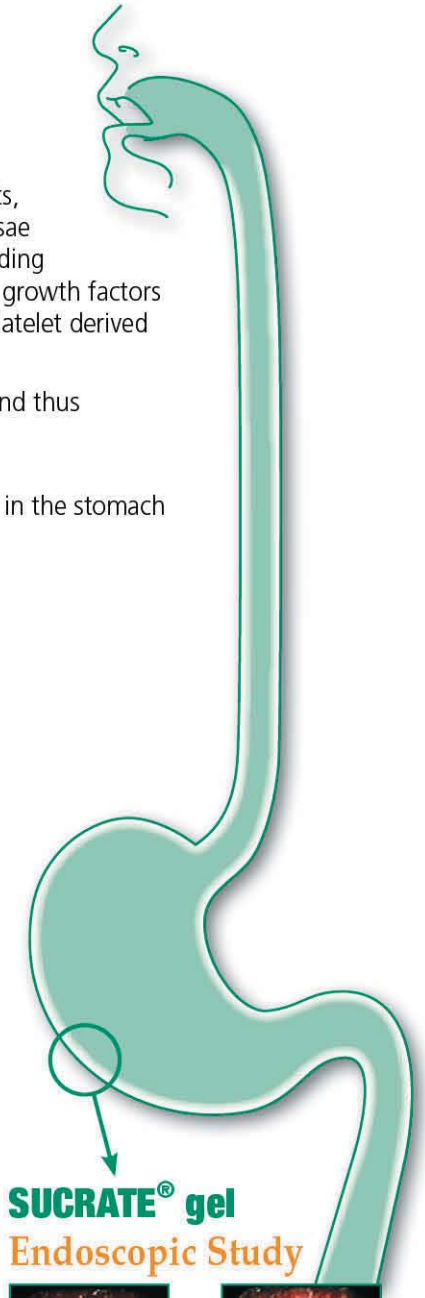

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Review of Newly Registered Oncology Drugs in Hong Kong

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ABSTRACT

There were 14 new oncology drugs registered in 2015 in Hong Kong including ceritinib, afatinib, ipilimumab, nivolumab, pembrolizumab, dabrafenib, vismodegib, enzalutamide, ibrutinib, idelalisib, obinutuzumab, brentuximab, pomalidomide and trastuzumab emtansine. These drugs covers five types of cancers including non-small cell lung cancer (NSCLC), skin cancer, prostate cancer, blood cancer and breast cancer. In this review, the indication, dosage, common side effects, proposed mechanism of action, related clinical studies and clinical benefits over existing agents of each new drug will be discussed.

Keywords: *Oncology drug, Cancer, Targeted therapy, Immunotherapy, Newly registered, Hong Kong*

INTRODUCTION

Based on the understanding of pathogenesis of cancer, various signalling pathways and the molecules that confer proliferation advantage in cancer have been identified. Targeted therapy poses an important dimension of cancer treatment due to the specificity to cancer cells and more favorable side effects profile over conventional chemotherapy. Therefore, more targeted therapies have been developed and included as the recommended cancer treatment in order to ameliorate the side effects of conventional chemotherapy. However, success of the targeted therapy depends on a number of factors, e.g. presence of molecular targets, inter- and intra-tumoral heterogeneity and mutations that cause resistance.[1] Different strategies have to be developed to overcome these obstacles, such as targeting of alternative signalling pathways and mutant molecules. Not surprisingly, the majority of the 14 oncology drugs registered in 2015 are targeted therapy designed to tackle drug resistances or improve treatment outcome. This review would help readers to familiarize with these new drugs in terms of their safety, efficacy and the difference from the existing therapy. The registered particulars of each drug would be based on the label information approved by the Hong Kong Drug Office (extracted from MIMS Hong Kong if available), in comparison with those approved by FDA and EMA. **Table 1** summarizes the date of approval in Hong Kong, certificate holder and the available dosage forms of the 14 new drugs.

A. Non – small cell lung cancer

Ceritinib (Zykadia®)

Ceritinib has obtained marketing authorization from FDA under accelerated approval in April 2014, and then EMA in May 2015.[3,4] The indication in Hong Kong is the same as that approved by FDA and EMA, i.e. for treatment of adult patients with anaplastic lymphoma kinase (ALK) – positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, which is also an ALK inhibitor. The recommended dosage is 750mg orally once daily and it should be taken on empty stomach, i.e. at least 2 hours before or after meal. No renal adjustment is required but hepatic adjustment is suggested.[5,6,7] Ceritinib is considered as a hazardous agent (Group 1 antineoplastic drugs) according to the NIOSH 2014 criteria so precautions are necessary for handling and disposal.[8]

Common side effects are anaemia, reduced appetite, rash, fatigue, nausea, vomiting and diarrhoea, which may occasionally be severe and require anti-diarrheals, anti-emetics or fluid replacement. Side effects that require dose reduction includes hepatotoxicity, interstitial lung disease (ILD) / pneumonitis, QTc interval prolongation, hyperglycaemia and bradycardia. In case necessary, the dose can be reduced by 150mg daily, and ceritinib should be discontinued permanently if a dose of 300mg daily cannot be tolerated. Since ceritinib is primarily metabolized by CYP3A4, CYP3A4 inhibitors, for example, grapefruit and grapefruit juice should be avoided. Dose reduction is suggested if concurrent use with strong CYP3A4 inhibitors is unavoidable.[5,6,7,8]

Ceritinib is a tyrosine kinase inhibitor (TKI) targeting ALK, insulin-like growth factor 1 receptor, insulin receptor and ROS1 among these targets, Ceritinib is most potent against ALK, a tyrosine kinase involved in the pathogenesis of NSCLC. Ceritinib also exhibited antitumor activity in EML4-ALK-positive NSCLC xenografts models with demonstrated resistance to crizotinib.[5,6,7]

Table 1. Summary of the manufacturer and available dosage forms of the new drugs[2]

Drug name	Date of approval in Hong Kong	Certificate Holder	Available dosage forms
Non-small-cell lung cancer			
Ceritinib (Zykadia®)	24 / 12 / 2015	Norvartis Pharmaceuticals (HK) Limited	150mg capsule
Afatinib (Giotrif®)	5 / 3 / 2015	Boehringer Ingelheim (HK) Ltd	20mg / 30mg / 40mg tablet
Skin cancer			
Ipilimumab (Yervoy®)	6 / 3 / 2015	Bristol-Myers Squibb Pharma (HK) Ltd	50mg/10ml, 200mg/40ml concentrate for solution for infusion
Nivolumab (Opdivo®)	22 / 12 / 2015	Bristol-Myers Squibb Pharma (HK) Ltd	40mg/4ml, 100mg/10ml concentrate for solution for infusion
Pembrolizumab (Keytruda®)	18 / 12 / 2015	Merck Sharp & Dohme (Asia) Ltd	50mg powder for injection, 100mg/4ml solution for injection
Dabrafenib (Tafinlar®)	4 / 3 / 2015	Novartis Pharmaceuticals (HK) Limited	50mg / 75mg capsule
Vismodegib (Erivedge®)	7 / 7 / 2015	Roche Hong Kong Limited	150mg capsule
Prostate cancer			
Enzalutamide (Xtandi®)	4 / 3 / 2015	Astellas Pharma Hong Kong Company Limited	40mg capsule
Blood cancer			
Ibrutinib (Imbruvia®)	26 / 10 / 2015	Johnson & Johnson (Hong Kong) Ltd	140mg capsule
Idelalisib (Zydelig®)	27 / 10 / 2015	Gilead Sciences Hong Kong Limited	100mg / 150mg tablet
Obinutuzumab (Gazyva®)	29 / 10 / 2015	Roche Hong Kong Limited	1000mg/40ml concentrate for solution for infusion
Brentuximab vedotin (Adcetris®)	2 / 3 / 2015	Takeda Pharmaceuticals (Hong Kong) Limited	50mg powder for concentrate for solution for infusion
Pomalidomide (Pomalyst®)	26 / 10 / 2015	Celgene Limited	1mg / 2mg / 3mg / 4mg capsule
Breast cancer			
Trastuzumab emtansine (Kadcyla®)	5 / 3 / 2015	Roche Hong Kong Limited	100mg / 160mg powder for concentrate for solution for infusion

The clinical efficacy of ceritinib was demonstrated in 2 global, multicentre, open-labelled, single-arm studies (ASCEND-1 and ASCEND-2). ASCEND-1 was a phase 1 study involving 246 patients with ALK – positive NSCLC, including 163 patients whose disease progressed during crizotinib therapy. The objective response rates (ORR) in ALK inhibitor–pretreated patients were 56%. The median progression – free survival (PFS) and overall survival (OS) in ALK inhibitor-pretreated were 6.9 months and 16.7 months respectively.[9] ASCEND-2 was a phase 2 study, evaluating the efficacy and safety of ceritinib in patients previously treated with at least one chemotherapy who progressed within 30 days from last treatment of crizotinib. One hundred and forty patients were recruited to receive 750mg ceritinib daily. The ORR was 38.6%. The PFS and OS were 5.7 months and 14.9 months respectively.[10]

Afatinib (Giotrif®)

Afatinib was first approved by FDA in July 2013,[3] followed by EMA in September 2013.[11] The approved indication is monotherapy for treatment of epidermal growth factor receptor (EGFR) TKI–naive patients with locally advanced or metastatic NSCLC carrying activating EGFR mutations. This is slightly different from the indication approved by US and Europe. FDA approved it for metastatic disease only while EMA for locally advanced or metastatic squamous NSCLC progressing on or after platinum–based chemotherapy. The recommended dosage is 40mg orally once daily, taken on an empty stomach to improve oral bioavailability. In Hong Kong, similar to EMA, the drug is recommended to be taken 3 hours before or 1 hour after food. Moreover, the tablet can be administered by dispersing it in noncarbonated drinking water without crushing it in case of difficulty in swallowing. By contrast, the US label information suggests to take the dose 1 hour before or 2 hours after meal. One point to note is that the dose can be titrated up to 50mg once daily as approved by EMA but not FDA or Hong Kong so afatinib 50mg tablet is only available in Europe. Renal adjustment was recommended by the US label information. The dose should be reduced to 30mg once daily if the estimated glomerular filtration rate (eGFR) is 15–29ml/min/1.73m^2. No dosage information was provided by the manufacturer for eGFR below 15 ml/min/1.73m^2. However, Hong Kong label follows EMA so no renal adjustment is recommended. No hepatic adjustment was provided either.[12,13,14] Afatinib is considered as a hazardous agent (Group 1 antineoplastic drug) according to NIOSH 2014 criteria. Single–gloving is recommended during administration of an intact tablet.[15]

Common side effects are epistaxis, paronychia, gastrointestinal toxicity, e.g. diarrhoea, stomatitis, cheilitis, skin and subcutaneous tissue disorder, e.g. acneiform dermatitis, pruritus, dry skin. Most frequently reported serious adverse effects include diarrhoea, vomiting, dyspnoea, fatigue, and hypokalaemia. Dose reduction is often needed in patients with diarrhoea, rash / acne, paronychia, and stomatitis. Afatinib is the substrate of BCRP and P-gp.[16] If a P-gp inhibitor has to be administered with afatinib, the dose of afatinib should be separated from the P-gp inhibitors by 6 hours (for P-gp inhibitors dosed twice daily) or 12 hours (for P-gp inhibitors dosed once daily) apart from afatinib, which follows the EMA label.[13,14] FDA instead suggested to reduce the dose by 10mg daily as tolerated.[12]

Afatinib irreversibly inhibits the tyrosine kinase autophosphorylation of EGFR (ErbB1), HER2 (ErbB2) and HER4 (ErbB4) by covalently binding to their kinase domains. **(Figure 1)** It demonstrates antiproliferative effect in cell lines expressing wild type EFGR or those expressing selected EGFR exon 19 deletion mutations or exon 21 L858R mutations in addition to those with a secondary T790M mutation.[12,13,14]

The clinical efficacy and safety of afatinib was mainly supported by a number studies. For example, LUX-LUNG 3 was a phase 3 study designed to compare the efficacy of cisplatin plus premetrexed chemotherapy with afatinib. 345 patients with stage IIIb / IV lung adenocarcinoma were enrolled. The median PFS for afatinib group and chemotherapy group was 11.1 months and 6.9 months respectively. Among those with deletion-19 or L858R mutations, the median PFS for afatinib group and chemotherapy group was 13.6 months and 6.9 months respectively. This demonstrated afatinib

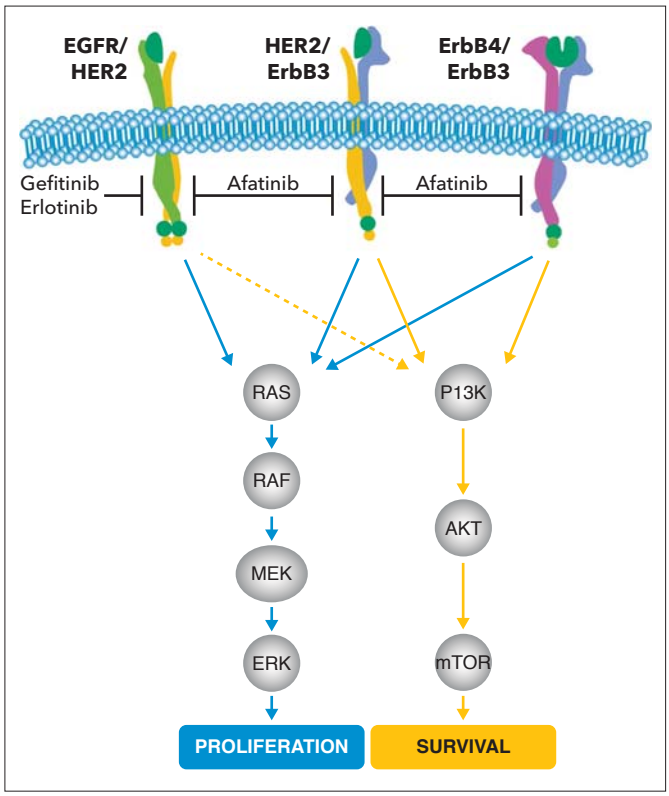

Figure 1: Mechanism of Afatinib. (Reprinted from permission of reference 15)

was associated in prolongation of PFS when compared to conventional chemotherapy in patients with advanced lung adenocarcinoma and EFGR mutations. Incidence of grade ≥3 adverse events was comparable in both groups but patient-reported outcome favoured the afatinib group, with better control of cough, dyspnoea and pain.[16] Afatinib also demonstrated improved efficacy when compared to other TKIs. Afatinib 40mg once daily significantly prolonged the median PFS and medial OS when compared to erlotinib 150mg once daily in patients with recurrent stage IIIb / IV squamous cell carcinoma.[17] LUX-LUNG 7 trial showed that afatinib resulted in significantly prolonged PFS, time to treatment failure and ORR in patients with recurrent or metastatic NSCLC and EGFR deletion-19 or L858A mutation, when compared with gefitinib.[18]

B. Skin cancer

Ipilimumab (Yervoy®)

Ipilimumab has gained approval by FDA and EMA in March 2011 and July 2011 respectively,[3,20] indicated for the treatment of unresectable or metastatic melanoma. The recommended dosage for metastatic melanoma is 3mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions. No renal or hepatic adjustment is provided by the manufacturer.[20,21,22]

Common adverse effects include rash, pruritus, diarrhoea, nausea, colitis, vomiting, weight loss, fatigue, headache and reduced appetite. Ipilimumab is also associated with immune–mediated adverse effects, e.g. dermatitis, endocrinopathy, enterocolitis, hepatitis and neuropathy. Ipilimumab has to be discontinued permanently in severe immune–mediated adverse effects. Systemic high-dose corticosteroid with or without additional immunosuppressive therapy may also be required. No CYP450 enzyme or other drug–metabolizing enzyme is needed for its metabolism so there is minimal drug interaction.[20,21,22]

Ipilimumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody which is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor. Interaction of antigen-presenting cells with CTLA-4 on activated, tumor-specific T-cells induces T-cell inhibiton. Therefore, ipilimumab restores T-cell activation and proliferation through blockade of CTLA-4, **(Figure 2)** thereby unleashing anti-tumor T-cell responses. Ipilimumab may also selectively deplete regulatory T-cells at the tumor sites, increasing the intratumoural T-effector / T-regulatory cell ratio which further boosts T cell-mediated anti-tumor responses.[20,21,22]

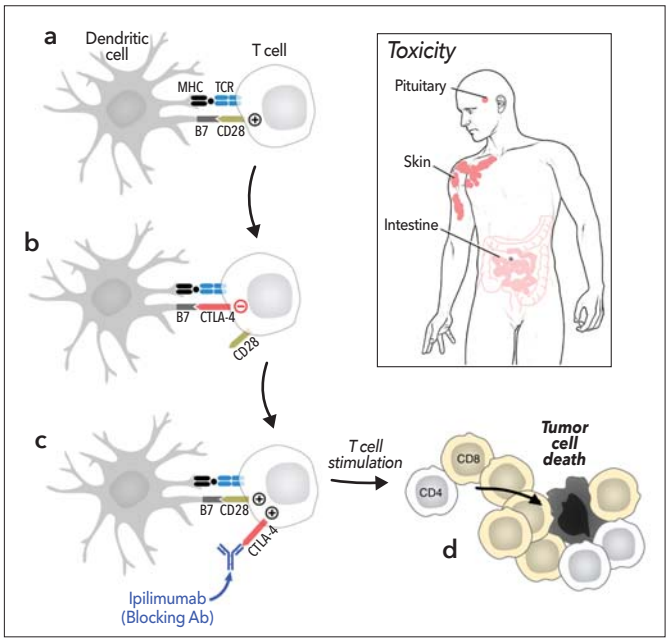

Figure 2: Mechanism of Ipilimumab. (Reprinted from permission of reference 23)

In a phase 3 placebo–controlled randomized clinical trial involving 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma, the median OS was significantly longer in patients given ipilimumab plus a glycoprotein 100 (gp100) vaccine (10.0 months) or ipilimumab alone (10.1 months), when compared with gp100 alone (6.4 months). Grade 3 or 4 immune–related adverse events were reported in 10–15% patients in the ipilimumab – gp100 group and in 3% in the gp100 group.[25] In another phase 3 trial conducted in 502 patients previously untreated metastatic melanoma, OS was significantly longer in the group receiving ipilimumab plus dacarbazine than in the group receiving dacarbazine alone (11.2 months vs. 9.1 months). Survival rate at 1, 2, and 3 years was also significantly higher in the ipilimumab–dacarbazine group. Grade 3 or 4 adverse events occurred in 56.3% patients treated with ipilimumab plus dacarbazine and in 27.5% patients in the control group.[26]

Nivolumab (Opdivo®)

Nivolumab has been approved by FDA under accelerated approval and EMA in March 2015 and June 2015 respectively.[3,27]. Similar to FDA of US, it is indicated for the treatment of patients with unresectable or metastatic melanoma which progresses following ipilimumab and a BRAF inhibitor if BRAF V600 mutation positive, and metastatic squamous NSCLC which progresses on or after platinum–

based chemotherapy. However, the type of NSCLC indicated is not stated. Moreover, advanced renal cell carcinoma after prior therapy is an additional indication approved in the EMA label. The recommended dosage of nivolumab is 3mg/kg intravenously over 60 minutes every 2 weeks until disease progression or intolerable toxicity. EMA label also recommends dosage for combination therapy with ipilimumab but this is not included in the Hong Kong label. No renal or hepatic adjustment is suggested.[27,28,30]

Nivolumab is generally well–tolerated with common mild side–effects such as fatigue, rash, pruritus, diarrhoea, nausea and reduced appetite. Immune–related adverse effects, e.g. pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, were also reported. Depending on the severity of the adverse reaction, corticosteroid may need to be administered while withholding the therapy. It must be permanently discontinued in case of life–threatening immune–related reactions. Nivolumab is not metabolized CYP450 enzymes or other drug–metabolizing enzymes so there is minimal drug interaction.[27,28,30]

Nivolumab is a fully human IgG4 monoclonal antibody that selectively inhibits the programmed death–1 (PD-1) receptors from binding to its ligands, PD-L1 and PD-L2. The binding of PD-1 ligands with the PD-1 receptor suppresses T cell proliferation and cytokine secretion. This PD-1-PDL1/2 pathway – mediated inhibition of anti–tumor response is boosted in caners in which PD-L1/2 are upregulated. **(Figure 3)** Thus, nivolumab potentiates the anti-tumor effect of the T cells through blockade of the PD-1 receptors.[27,28,30]

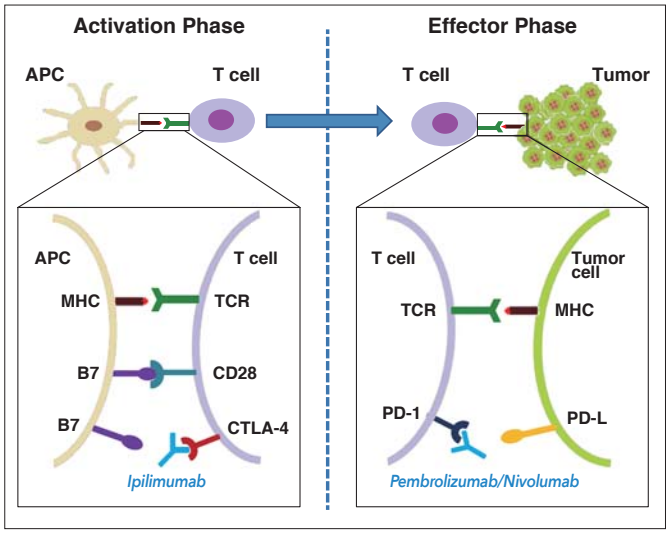

Figure 3: Mechanism of Pembrolizumab / Nivolumab. (Reprinted from permission of reference 29)

The clinical efficacy and safety were studied in several clinical trials. In a randomized, double–blind, phase 3 study, nivolumab alone or in combination with ipilimumab resulted in significantly longer median PFS than ipilimumab alone (6.9 months versus 11.5 months versus 2.9 months) in 945 previously untreated patients with unresectable stage III / IV melanoma. Combination therapy also resulted in significantly prolonged PFS in a subset of patients with PD-L1 negative tumours, compared with nivolumab alone (11.2 months vs. 5.3 months). The ORRs were 57.6%, 43.7% and 19.0% with nivolumab plus ipilimumab, nivolumab alone and ipilimumab alone respectively.[32] However, the incidence of grade 3 or 4 toxicity was increased with the combination therapy, compared with ipilimumab alone.[33] In another randomized, open-labelled study, 272 patients with metastatic squamous NSCLC were enrolled to received either nivolumab 3mg/kg intravenously every 2 weeks or docetaxel 75mg/m2 every 3 weeks. The nivolumab group demonstrated significantly prolonged PFS than the docetaxel group (9.2 months vs. 6.0 months). Moreover, lower rate of treatment-related adverse events of grade 3 or 4 was reported in the nivolumab group than in the docetaxel group (7% vs. 55%).[34]

Pembrolizumab (Keytruda®)

Pembrolizumab, approved by FDA and EMA in September 2014 and July 2015 respectively,[3,35] is indicated for the treatment of unresectable or metastatic melanoma which progresses on or after ipilimumab and if BRAF V600 mutation–positive, a BRAF inhibitor. While it is also indicated for patients with metastatic NSCLC whose tumour expresses PD-L1 in the US under accelerated approval, only the indication for melanoma is approved in Hong Kong. The recommended dosage is 2mg/kg administered intravenously over 30 minutes every 3 weeks until disease progression or intolerable toxicity. No renal or hepatic adjustment is suggested.[36,37,38]

The most common adverse effects reported were fatigue, cough, rash, pruritus, diarrhoea, arthralgia and nausea, which were generally mild to moderate. Rarely, pembrolizumab is associated with immune–mediated reactions resembling other immunoglobulins, e.g. autoimmune hepatitis, pneumonitis and endocrinopathy (around 1%). Since its metabolism does not involve any drug – metabolizing enzymes, drug interaction is minimal.[36,37,38]

Pembrolizumab is a humanized anti-PD-1 monoclonal antibody with the same mechanism of action as nivolumab. **(Figure 3)** [36,37,38]

In a randomized, controlled phase 3 study, 834 patients with advanced, ipilimumab-naive melanoma were assigned in a 1:1:1 ratio to receive pembrolizumab at 10mg/kg every 2 weeks or every 3 weeks or 4 doses of ipilimumab at 3mg/kg every 3 weeks. The estimated 6-month PFS rates for pembrolizumab every 2 weeks (47.3%) and every 3 weeks (46.4%) were significantly higher than that for ipilimumab (26.5%), so as the estimated 12-month PFS rates. The pembrolizumab groups also had a lower rate of adverse events of grade 3 to 5 than the ipilimumab group (13.3% and 10.1% vs. 19.9%).[39] Among anti-PD-1 antibodies, pembrolizumab has the highest affinity for PD-1, which theoretically implies greater potency as the same physiological response can be triggered by a lower concentration of drug. However, whether the affinity for the receptor translates into clinical efficacy remains to be answered by more clinical trials.[40]

Dabrafenib (Tafinlar®)

Dabrafenib has received the approval from FDA and EMA in March 2013 and August 2013 respectively.[3,41] While it is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation (monotherapy or in combination with trametinib) or V600K mutation (in combination with trametinib) in the US and Europe, only monotherapy is approved by Hong Kong. Since the efficacy of dabrafenib in wild-type BRAF melanoma has not been established, the V600 mutation status has to be confirmed with an approved test before initiation of dabrafenib. The recommended dosage is 150mg orally twice daily, taken on empty stomach, i.e. 1 hour before or 2 hours after meal,

to improve absorption. No renal or hepatic adjustment is necessary.[42,43,44] It is classified as a hazardous agent according to NIOSH 2014 criteria so single gloving is recommended during administration of intact capsules.[45]

Common side–effects are papilloma, pyrexia, fatigue, nausea, headache, chills, rash, arthralgia, hypertension, vomiting and cough. Depending on the severity, dose modification may be necessary when some of the adverse effects, e.g. pyrexia, skin toxicity, uveitis, are reported. Dose is reduced by 25mg twice daily (50mg daily). It has to be permanently discontinued when the patient cannot tolerate 50mg twice daily. Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Therefore, when co-administration with strong enzyme inhibitors or inducers is deemed unavoidable, loss of efficacy and adverse effects should be monitored closely. Antacid and gastric acid suppressants may also reduce the bioavailability of dabrafenib by reducing its solubility so these drugs should be avoided during treatment with dabrafenib if possible, though no formal study has been conducted to evaluate the effect of pH on the absorption of dabrafenib.[42,43,44]

Dabrafenib is a RAF kinases inhibitor, which inhibits some mutated forms of BRAF kinases, primarily BRAF V600E and BRAF V600K. Since BRAF V600 mutations result in constitutive activation of the RAS/RAF/MEK/ERK pathway and V600E accounts for approximately 90% of the BRAF mutations in melanoma, dabrafenib can inhibit tumor growth.[42,43,44]

In an open-labelled, phase 3 study, 250 patients with previously untreated BRAF V600E mutation–positive melanoma were randomly assigned to receive dabrafenib (150mg twice daily, orally) or dacarbazine (1000 mg/m^2 intravenously every 3 weeks). The median PFS for dabrafenib (5.1 months) was significantly longer than that for dacarbazine (2.7 months). It was also speculated that dabrafenib may be less likely to cause cutaneous adverse effects than vemurafenib, another BRAF kinase inhibitor due to the low specificity of dabrafenib for wild–type BRAF and CRAF or different pharmacological properties. However, the dabrafenib group had a higher incidence of adverse events (grade 2 or above) than the dacarbazine group (53% vs. 44%).[46] In another double-blinded, phase 3 study, 423 patients with previously untreated BRAF V600E or V600K mutation–positive unresectable or metastatic melanoma were enrolled to receive dabrafenib (150mg orally twice daily) and trametinib (2mg orally once daily) or dabrafenib (150mg orally twice daily) alone. The median PFS for the combination–therapy group (11.0 months) was significantly longer than the monotherapy group (8.8 months). This establishes the combination of dabrafenib and trametinib as the standard targeted therapy for BRAF V600 mutation–positive melanoma.[47]

Vismodegib (Erivedge®)

Vismodegib is indicated for the treatment of adults with metastatic basal cell carcinoma (BCC), or locally advanced BCC that has recurred following surgery, or who are not candidates for surgery or radiation. Hong Kong label follows the same indication.[45,46,47] It has gained the marketing authorization from FDA and EMA in January 2012 and July 2013 respectively.[3,51] The recommended dosage is 150mg orally once daily, taken without regards to meal. No renal or hepatic adjustment is necessary.[48,49,50] It is a hazardous agent according to NIOSH 2014 criteria so single gloving is recommended for administration of intact capsules.[52]

Common side–effects include muscle spasm, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhoea / constipation and reduced appetite. Vismodegib is only minimally metabolized by CYP2C9 and CYP3A4 so clinically significant interaction with CYP450 inducers and inhibitors is not expected.[48,.49,50]

In BCC, the Hedgehog pathway is constitutively active because a mutation causes PTCH1 to lose its ability to inhibit Smoothened homologue (SMO), the transmembrane protein involved in the Hedgehog signal transduction.[53] Vismodegib is a small – molecule inhibitor of Hedgehog pathway, which binds to and inhibits SMO. This blocks the activation and nuclear localization of Glioma–Associated Oncogene (GLI) transcription factor and hence induction of Hedgehog target genes. Thus, vismodegib can inhibit the proliferation, survival and differentiation of tumor cells.[48,49,50]

In a multicentre, nonrandomized, open-label, 2-cohort trial, patients with metastatic BCC (n=33) or locally advanced BCC which was unresectable or inappropriate for surgery (n=63) received vismodegib 150mg orally once daily. The ORR in metastatic BCC was 30% while that for locally advanced BCC was 43%, which exceeds the primary hypothesized ORR for metastatic BCC (>10%) and locally advanced BCC (>20%). The median duration of response was 7.6 months in both cohorts.[54]

C. Prostate cancer

Enzalutamide (Xtandi®)

Enzalutamide, approved by the FDA and EMA in August 2012 an June 2013 respectively,[3,55] is indicated for the treatment of patients with metastatic, castration–resistant prostate cancer, whose disease has progressed on or after docetaxel therapy. The indication in EMA label also states that enzalutamide can be used in patients who are chemotherapy–naive, while FDA label does not specify the past medical history. The recommended dosage is 160mg orally once daily, and can be taken without regards to meal. The medical castration with an LHRH analogue should be continued during enzalutamide therapy unless the patient is surgically castrated. No renal or hepatic adjustment is necessary.[56,57,58] Since it is classified as hazardous agents according to NIOSH 2014 criteria, precautions should be carried out during handling and disposal.[56]

The most common adverse effects are asthenia / fatigue, hot flush, headache, hypertension, reduced appetite and constipation / diarrhoea. Some serious adverse effects include seizure and posterior reversible encephalopathy syndrome (PRES). There are limited safety data in patients with predisposing factors for seizure. Enzalutamide must be permanently discontinued if the patient experiences seizure or PRES. The metabolism of the parent compound is primarily via CYP2C8 and CYP3A4 while that of the active metabolite is mainly via CYP2C8. Enzalutamide is also a strong CYP3A4 inducer and moderate CYP2C9 and 2C19 inducer. If coadministration with strong CYP2C8 inhibitors is unavoidable, Hong Kong label suggests that the dose of enzalutamide should be reduced to 80mg once daily. No dosage adjustment is needed for coadministration with CYP3A4 inducers because CYP3A4 is not the major metabolizing enzyme, which follows the EMA's. However, the FDA label instead suggests increasing the dose to 240mg once daily for coadministration with CYP3A4 inducers.[56,57,58]

Enzalutamide is a potent androgen receptor inhibitor, which competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA.[56,57,58]

In the PREVAIL trial, which is a double-blind, phase 3 trial, chemotherapy–naive patients receiving enzalutamide 160mg daily resulted in significantly higher rate of radiographic PFS at 12 months than patients receiving placebo (65% vs. 14%).[60] Another phase 3 trial showed that median OS in patients who previously received chemotherapy was significantly higher in the group who took enzalutamide 160mg daily (18.4 months) than the placebo group (13.6 months).[61] Unlike bicalutamide, enzalutamide does not possess agonistic features at the androgen receptor that would trigger target gene expression, which thereby may contribute to the greater efficacy of enzalutamide. A randomized, double-blind, phase 2 study showed that enzalutamide 160mg daily resulted in significantly prolonged median PFS, when compared to bicalutamide 50mg daily (19.4 months vs. 5.7 months). Both treatment groups had similar rate of adverse events of grade ≥3 and adverse events resulting in death.[59] Compared to abiraterone, which is a CYP17 enzyme inhibitor, enzalutamide does not need to be co-administered with prednisolone which eliminates the adverse effects of long–term use of corticosteroid.[63]

D. Blood cancer

Ibrutinib (Imbruvica®)

Ibrutinib has been approved by FDA and EMA in February 2014 and October 2014 respectively for various indications.[3,61] In Hong Kong, it is indicated for salvage treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least 1 prior therapy or frontline treatment in those with 17p deletion or TP53 mutation or patients unsuitable for chemo–immunotherapy. On the other hand, FDA and EMA also approved ibrutinib for relapsed or refractory mantle cell lymphoma and Waldenström's macroglobulinemia but not CLL with TP53 mutation. The recommended dosage is 420mg orally once daily, and can be taken without regards to meal. The Hong Kong label follows the hepatic adjustment suggested by EMA, i.e. 280mg daily for patients with mild liver impairment (Child-Pugh class A), 140mg daily for moderate impairment (Child-Pugh class B), and not recommended to use in severe impairment (Child-Pugh Class C). FDA label instead suggested to reduce the dose to 140mg daily in mild impairment and not to use in moderate to severe impairment. No renal adjustment is necessary.[65,66,67] Ibrutinib is a hazardous agent according to NIOSH 2014 criteria so single gloving is recommended for administration of an intact capsule.[68]

Ibrutinib is associated with haematological toxicity, e.g. gastrointestinal bleeding, intracranial haemorrhage, haematuria, neutropenia, contusion and epistaxis, atrial fibrillation / flutter, and infection, e.g. sepsis, bacterial, viral or fungal infection. In case of severe side–effects, ibrutinib should be withheld and may be reinitiated at a lower starting dose. Dosage adjustment can be achieved by reducing the dose by 140mg daily. Other adverse effects include nausea, vomiting, diarrhoea, headache, dizziness and rash. Tumour lysis syndrome has also been reported. Ibrutinib is metabolized primarily by CYP3A4 so lack of efficacy or signs of toxicity should be closely monitored if co-administration with enzyme inducers or inhibitors is unavoidable.[65,67,68]

Ibrutinib is a potent, small–molecule inhibitor of Bruton's tyrosine kinase (BTK), which is an important signalling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathway. **(Figure 4)** The inhibition of the BCR pathway thus inhibits malignant B cell proliferation and survival, as well as trafficking, chemotaxis and adhesion.[65,67,68]

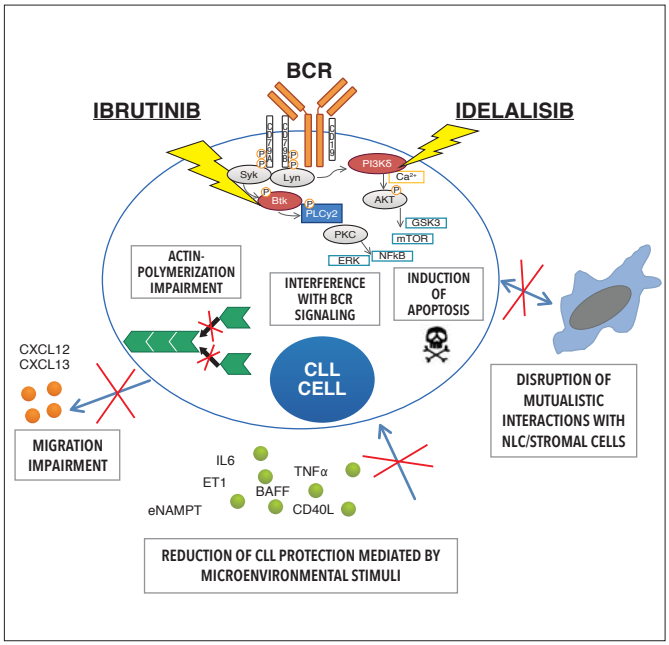

Figure 4: Mode of actions of Ibrutinib and Idelalisib. (Reprinted from permission of reference 66)

In a randomized, multicentre, open-label phase 3 study, 391 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) were enrolled to received either ibrutinib 420mg orally daily or intravenous ofatumumab, another FDA-approved treatment for refractory CLL. Ibrutinib significantly improved median PFS, with the median not reached at a median follow – up of 9.4 months, compared with a median PFS of 8.1 months with ofatumumab. The OS at 12 months in ibrutinib group is significantly longer than the ofatumumab group (90% vs. 81%). ORR was also significantly higher in the ibrutinib group (42.6%) than in the ofatumumab (4.1%). Similar effects were found in the group with 17p13.1 deletion or resistance to purine analogues. However, more patients in the ibrutinib group had at least 1 adverse event of grade 3 or higher than in the ofatumumab (57% vs. 47%).[70] In another randomized, multicentre, open-label, phase 3 study, previously untreated patients were assigned to either receiving ibrutinib or chlorambucil. The ibrutinib group showed a significantly prolonged PFS and OS, and higher ORR. Moreover, fewer patients in the ibrutinib group discontinued treatment due to adverse events than the chlorambucil group (9% vs. 23%).[71]

Idelalisib (Zydelig®)

Idelalisib, approved by FDA and EMA in July 2014 and September 2014,[3,72] is indicated for three types of blood cancers, i.e. as combination therapy with rituximab for the treatment of relapsed CLL, and as monotherapy for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma (FL) and SLL in patients who have received at least 2 prior systemic therapy. The indication for FL and SLL was approved by accelerated approval by FDA. The recommended dosage is 150mg orally twice daily, taken without regards to meal. No renal adjustment is necessary. For hepatic adjustment

as suggested by the FDA label, the dose should be reduced to 100mg twice daily if ALT/AST exceeds 5 – 20 times the ULN or bilirubin exceeds 3–10 times the ULN. It should be discontinued permanently if ALT/AST and bilirubin are beyond 20 times and 10 times the ULN respectively. This is different from that in the EMA label. Only ALT/AST, but not bilirubin, is suggested to be the indicator for hepatic adjustment.[73,74] Idelalisib is a hazardous agent according to the NIOSH 2014 criteria so single gloving is recommended for administration of intact tablets.[75]

The most common adverse effects are diarrhoea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills and rash. Dose reduction or discontinuation is recommended if there is hepatotoxicity, diarrhoea, neutropenia or pneumonitis, rash, or thrombocytopenia, depending on the severity. Idelalisib is also associated with fatal infection, including opportunistic infection, e.g. pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) infection so prophylaxis for PJP and regular screening for CMV are necessary. The metabolism is primarily via CYP3A4 and idelalisib is a strong inhibitor of CYP3A4. If co-administration with the enzyme inducers or inhibitors is unavoidable, signs of toxicity or loss of efficacy should be monitored.[73,74]

Idelalisib is a potent small molecule inhibitor of the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ), which is hyperactive in B-cell malignancies. **(Figure 4)** It thus results in apoptosis and inhibition of proliferation in cell lines derived from malignancy B cells and in primary tumor cells. It also inhibits homing and retention of malignant B cells in lymphoid tissues and bone marrows through inhibition of chemokine receptors CXCR4 and CXCR5 signalling.[73,74]

In a multicentre, randomized, double-blind, placebo-controlled, phase 3 study, 220 patients with relapsed CLL and comorbidities that render them not suitable for standard chemotherapy received idelalisib plus rituximab or rituximab plus placebo. The median PFS in the idelalisib group was not reached and that in the placebo group was 5.5 months. The ORR and OS at 12 months was also improved in the idelalisib group (81% vs. 13%, 92% vs. 80%). This demonstrated the clinical efficacy of idelalisib as combination therapy with rituximab for the treatment of CLL.[76] The accelerated approval granted to FL and SLL was based on improved ORR. In a single-group, open-label, phase 2 study, 72 patients with FL and 26 patients with SLL who had received a median of 4 prior therapies, were administered idelalisib 150mg twice daily until disease progression or patient withdrawal. The ORR for FL and SLL was 54% and 58% with the median time to response of 1.9 months and median duration of response of 12.5 months, respectively.[73,77] However, FDA has issued safety alerts on the increased rate of adverse events, including death, in clinical trials with idelalisib in combination with other oncology medications. Gilead, the manufacturer, has confirmed that 6 clinical trials in patients with CLL, FL and SLL were stopped and the findings are currently under review by the FDA.[78]

Obinutuzumab (Gazyva®)

FDA and EMA have granted marketing authorization to obinutuzumab in November 2013 and July 2014,[3,79] indicated for the treatment of previously untreated CLL in combination with chlorambucil, where EMA label specifies that the patients should have comorbidities making them unsuitable for full-dose fludarabine-based therapy, and the treatment of FL in combination with bendamustine followed by obinutuzumab monotherapy in patients whose disease has progressed on, or after a rituximab–containing regimen. However, only the EMA approved indication for CLL is approved in Hong Kong. The recommended regimen consists of 6 cycles with 28 days per cycle. In the 1st cycle, 100mg, 900mg and 1000mg are respectively administered via intravenous infusion on Day 1, Day 2 (or Day 1 continued), and Day 8 & 15. In the 2nd to 6th cycle, 1000mg is administered via intravenous infusion on Day 1. No renal or hepatic adjustment is suggested.[80,81,82]

Obinutuzumab is associated with significant infusion–related reactions so premedication with oral analgesic, antihistamine and intravenous corticosteroid is necessary Antihypertensive medication should also be withheld due to hypotensive risk during infusion. Other common side–effects include pyrexia, cough, nausea, and arthralgia. Haematological toxicities, e.g. neutropenia, thrombocytopenia and anaemia are also common. Due to impaired immunity, serious infection, e.g. hepatitis B reactivation, progressive multifocal leukoencephalopathy (PML) has also been reported. Patients with a high tumour burden and/or a high circulating lymphocyte count (>25x10^9/L) and/or renal impairment (CrCl<70ml/min) are at high risk of tumour lysis syndrome. Adequate hydration and allopurinol or rasburicase should be given 12–24 hours prior to each infusion. The metabolism of obinutuzumab has not been formally studied and the manufacturer does not provide any information about drug interaction.[80,81,82]

Obinutuzumab is a recombinant monoclonal humanized and glycoengineered Type-II anti-CD20 antibody of the IgG isotype. The main pharmacological targets are the extracellular loop of the CD20 transmembrane antigen on the surface of pre B- and mature B-lymphocytes. It mediates B-cell lysis upon binding to CD20 through engagement of immune effector cells, activation of intracellular death signalling pathway and activation of the complement cascade. Glycoengineering of the Fc part of obinutuzumab increases its affinity for FcγRIII receptors on immune effector cells, e.g. natural killer (NK) cells, macrophages and monocytes.[80,81]

In a three-arm, open-label, active-controlled, randomized, multicentre, phase 3 study, 781 patients with previously untreated CLL were enrolled to receive chlorambucil, obinutuzumab plus chlorambucil or rituximab plus chlorambucil. Both the obinutuzumab and rituximab groups had improved ORR and median PFS than the chlorambucil – alone group. When the obinutuzumab group was compared with the rituximab group, the obinutuzumab significantly prolonged median PFS (26.7 months vs. 15.2 months) and ORR (79.6% vs. 66.3%). The obinutuzumab group had a higher rate of early discontinuation than the rituximab group due to infusion – related reaction but the rate of death due to adverse events was lower in the obinutuzumab group than in the rituximab and chlorambucil–alone group (4% vs. 6% and 9%).[80,81] Although the mechanism of action of obinutuzumab appears different from that of rituximab and obinutuzumab was found to be superior to rituximab when combined with chlorambucil, studies have not determined whether obinutuzumab can be used in tumours with resistance to rituximab.[84]

Brentuximab vedotin (Adcetris®)

Brentuximab vedotin has respectively received the marketing authorization from FDA and EMA in August 2011 and October 2012.[3,81] The indications approved by Hong Kong Drug

Office followed those approved by EMA, i.e. for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT), or at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option, and the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). In FDA label, it was also approved for the treatment for patients with HL at high risk of relapse or progression after ASCT and the indication for sALCL was granted accelerated approval. The recommended dosage is 1.8mg/kg up to 180mg administered via intravenous infusion over 30 minutes every 3 weeks. The treatment should continue until disease progression or intolerable toxicity. However, if patient achieves stable disease or better, a minimum of 8 cycles and up to a maximum of 16 cycles should be received.[86,87,88] The recommendation on renal and hepatic adjustment in the FDA and EMA label is different. For renal adjustment, FDA label suggests not to use brentuximab in patients with severe renal impairment (CrCl <30ml/min), EMA label suggests to reduce the dose to 1.2 mg/kg administered intravenously over 30 minutes every 3 weeks in severe renal impairment without stating the parameters. For hepatic adjustment, FDA label suggests to reduce the dose to 1.2mg/kg in patients with Child-Pugh A and not to use in those with Child-Pugh B or C but EMA label only suggests to reduce the dose to 1.2mg/kg without specifying the severity of liver impairment.[86,88] It is a hazardous agent according to NIOSH criteria so precautions for handling and disposal should be practiced.[90]

The most common adverse effects include peripheral neuropathy, haematological toxicity, e.g. neutropenia, thrombocytopenia and anaemia, gastrointestinal disorders, e.g. nausea, diarrhoea, vomiting, rash and cough. Hepatotoxicity, peripheral neuropathy and neutropenia may be resolved by dose reduction. Brentuximab is also associated with tumour lysis syndrome, PML and serious dermatological reactions, e.g. Steven Johnson Syndrome (SJS) and toxic epidermal necrosis (TEN). The active compound in brentuximab, monomethylauristatin E (MMAE), is the substrate of CYP3A4 and P-gp so concomitant administration with CYP3A4 and P-gp inhibitors may increase the risk of neutropenia.[86,88]

Brentuximab vedotin is an antibody drug conjugate (ADC) which consists of a CD-30 specific chimeric IgG1 antibody (cAC10), MMAE, and a protease cleavable dipeptide linker that covalently conjugates cAC10 and MMAE. **(Figure 5)** CD30 is expressed as an antigen on the surface of malignant cells in classical HL and sALCL. Binding of the ADC to the CD-30 expressing cells initiates the internalization of the ADC-CD30 complex, which then releases the MMAE within the cell. The microtubule network would be disrupted by MMAE upon binding to the tubulins. This results in cell cycle arrest and apoptosis of the CD-30 expressing cells. Since CD-30 is expressed irrespective of prior transplant status or resistance to multi-agent chemotherapy, brentuximab vedotin is able to overcome the resistance to chemotherapy.[86,88]

In a multinational, open-label, phase 2 study, 102 patients with relapsed or refractory CD30–positive HL after ASCT were recruited to receive brentuximab vedotin 1.8mg/kg intravenously every 3 weeks for up to 16 cycles. The ORR was 75% with complete response (CR) in 34% of patients. The median PFS for all patients was 5.6 months while that for those with CR was CR was 20.5 months, which was significantly longer than that achieved with the most recent therapy.[86] In another open-label, single-arm, multicentre, phase 2 study, 58 patients with relapsed or refractory sALCL were enrolled to receive brentuximab vedotin 1.8mg/kg intravenously every 3 weeks. The ORR was 86% with 57% of patients achieving CR. The median PFS for all patients and those with CR was 13.3 months and 14.3 months respectively, compared with a median PFS of 5.9 months after the most recent therapy. The median OS was not reached at the time of analysis.[92]

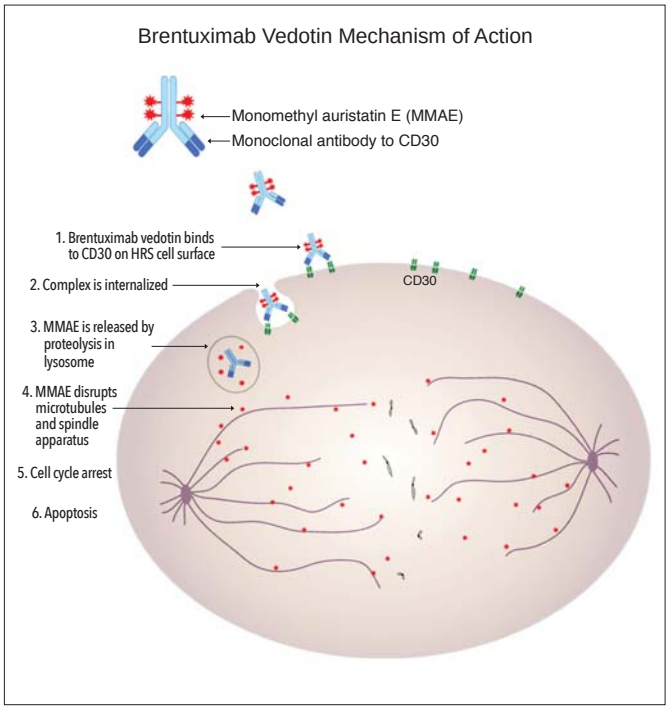

Figure 5: Mechanism of action of brentuximab vedotin. (Reprinted from permission of reference 87)

Pomalidomide (Pomalyst®)

Pomalidomide, approved by FDA and EMA in February 2013 and August 2013 respectively,[3,93] is indicated for treatment of multiple myeloma (MM) in combination with dexamethasone in patients who have received at least 2 prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. The recommended dosage is 4mg orally once daily, taken without regards to meal, on Day 1 to 21 of repeated 28–day cycles until disease progression or intolerable toxicity. Dexamethasone 40mg orally once daily should be taken on Day 1, 8, 15 and 22 of each 28–day treatment cycle. Renal and hepatic adjustments are only suggested by the FDA label. The dose should be reduced to 3mg daily, taken after completion of dialysis procedure on haemodialysis day in patients with severe renal impairment requiring dialysis. For hepatic adjustment, the dose should be respectively reduced to 3mg and 2mg daily in mild to moderate and severe liver impairment.[94,95] Since it is a hazardous agent according to NIOSH criteria, single gloving is recommended for administration of intact capsules.[96]

Pomalidomide is associated with venous and arterial thromboembolism, hepatotoxicity, haematological disorders, e.g. thrombocytopenia, neutropenia, anaemia, neuropathy and tumour lysis syndrome. Hepatotoxicity, thrombocytopenia and neutropenia can be resolved by dose reduction. Other mild side–effects include nausea, diarrhoea / constipation, vomiting, pyrexia, cough, headache, dizziness, rash and

pruritus. Pomalidomide is a major substrate of CYP1A2 so the dose of pomalidomide should be reduced by 50% when it is co-administered with strong CYP1A2 inhibitors.[94,95]

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic properties. It synergises with dexamethasone to inhibit proliferation and induce apoptosis of haematopoietic tumour cells, which acts on the lenalidomide-resistant cell lines as well. It also enhances T cell- and NK cell–mediated cytotoxicity and inhibits angiogenesis and the production of pro-inflammatory cytokines, e.g. TNF-α, IL-6.[94,95,91]

In a multicentre, open-label, randomized phase 2 trial, 221 patients with MM who had received at least 2 prior therapies including lenalidomide and bortezomib and had progressed within 60 days of their last therapy were enrolled to received either pomalidomide plus low-dose dexamethasone or pomalidomide alone. The combination therapy group has significantly prolonged PFS (4.2 months vs. 2.7 months), higher ORR (33% vs. 18%) and higher median OS (16.5 months vs. 13.6 months), when compared with the monotherapy group.[97] In another multicentre, open-label, randomized phase 3 study, 455 patients who fitted the indication of pomalidomide were assigned to receive either pomalidomide plus low-dose dexamethasone or high-dose dexamethasone alone. The median PFS in the pomalidomide group was significantly longer than the high-dose dexamethasone group (4.0 months vs. 1.9 months). The median OS and ORR were also significantly longer and higher in the pomalidomide group than in the high-dose dexamethasone group (12.7 months vs. 8.1 months; 31% vs. 10%). However, serious adverse events, which required hospitalization or resulted in disability or incapacity, occurred more frequently in the pomalidomide group than the high-dose [98]

E. Breast cancer

Trastuzumab emtansine (Kadcyla®)

Trastuzumab emtansine, approved by FDA and EMA respectively in February 2013 and November 2013,[3,99] indicated for the treatment of HER2-positive, metastatic breast cancer as a single agent in patients who previously received trastuzumab and a taxane, separately or in combination. Patient should have either received prior therapy for metastatic disease or have progression during or within 6 month of completing adjuvant therapy. Hong Kong label follows the same indication. The recommended dosage is 3.6 mg/kg administered via intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Trastuzumab emtansine should not be substituted for or with trastuzumab. Adjustment based on AST/ALT and total bilirubin is necessary. No renal adjustment is provided by the manufacturer.[101,102,103] It is classified as hazardous agents according to NIOSH criteria so there should be precautions for handling and disposal.[103]

The most common adverse effects include thrombocytopenia, nausea, constipation, fatigue, musculoskeletal pain, headache and haemorrhage. Dose reduction, treatment interruption or permanent discontinuation may be necessary depending on the severity of hepatotoxicity, left ventricular dysfunction, thrombocytopenia and peripheral neuropathy. If interstitial lung disease is reported, trastuzumab emtansine should be discontinued permanently. Due to the risk of infusion – related reaction, the first cycle should be administered over 90 minutes and the patients should be observed for at least 90 minutes after infusion. If previous infusions were well tolerated, subsequent cycles can be administered over 30 minutes with observation for at least 30 minutes after infusion. Unlike trastuzumab, trastuzumab emtansine is metabolized primarily by CYP3A4 so administration of strong CYP3A4 inhibitors should be separated from trastuzumab emtansine by approximately 3 half-lives of the inhibitors. Otherwise, patients should be closely monitored for signs of toxicity.[101,102,103]

Trastuzumab emtansine is a HER2-targeted antibody-drug conjugate, which incorporate trastuzumab as the anti-HER2 antibody and DM-1 (a maytansine derivative). **(Figure 6)** Trastuzumab emtansine has the mechanism of action of both trastuzumab and DM-1. Upon binding to the HER2 receptor, it undergoes receptor-mediated internalization which releases DM-1 within the malignant cells. DM-1 is a microtubule inhibitor and results in cell cycle arrest and apoptosis. The linker between DM-1 and trastuzumab, MCC linker, is designed to increase targeted delivery of DM-1 and reduce systemic exposure of DM-1.[101,102]

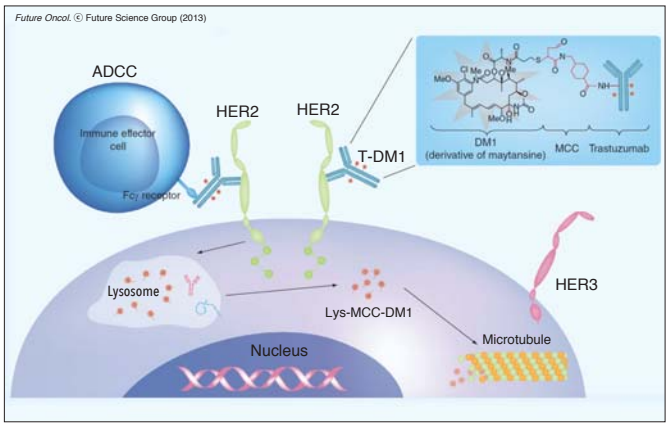

Figure 6: Mechanism of action of Trastuzumab emtansine. (Reprinted from permission of reference 100)

In a randomized, open-label, international trial, 991 patients whose conditions fulfil the indication of trastuzumab emtansine were enrolled to receive trastuzumab emtansine or lapatinib plus capecitabine. The trastuzumab emtansine group demonstrated significantly prolonged median PFS (9.6 months vs. 6.4 months), median OS (30.9 months vs. 25.1 months) and higher ORR (43.6% vs. 30.8%), when compared with the lapatinib group. The trastuzumab emtansine group also had a lower rate of adverse events of grade 3 or above than the lapatinib group (57% vs. 41%).[104]

CONCLUSION

With the advent of targeted therapy, new options are available to tackle chemo-resistant cancers. Not only do these agents show high efficacy against specific types of cancers, their adverse reactions are generally also more favorable than conventional chemotherapeutic agents. However, up till now, most of such agents are used as adjunctive or salvage therapies. It also requires costly genetic tests in order to confirm the presence of cellular therapeutic targets. In this connection, it is essential that pharmacists can provide updated information on the therapeutic effects and expected adverse reactions to both healthcare professionals and patients.

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Considering Cognitive Function Treatment in Major Depressive Disorder

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ABSTRACT

There are many people worldwide that suffer from depression. Both pharmacological and non-pharmacological therapies are available to treat patients with major depressive disorder. More recently, it has been noted that cognitive function plays a major role in major depressive disorder and that a novel serotonin reuptake inhibitor, vortioxetine has been shown to improve cognitive functioning. Other medications also have pro-cognitive effects in certain cognitive domains (eg. duloxetine) and some need more studies to ascertain their efficacy in improving cognition. A gold standard for measuring cognitive function in major depressive disorder has not been well established. When choosing antidepressant treatment for a patient, it is important to be sensitive to the patient the concerns and needs.

Keywords: *major depressive disorder, vortioxetine, cognitive function, depression*

INTRODUCTION

In Hong Kong, studies show that there are over 300 thousand depressive patients.(1) According to the World Health Organisation, there are more than 350 million people of all ages that suffer from depression and it is the leading cause of disability worldwide which is a major contributor to the global burden of disease.(2) Mild depression can affect a person's daily activities whereas severe depression may lead to suicide attempts. Major depressive disorder (MDD) is a challenging clinical condition where only about 30-40% of patients achieve full remission with first-line therapy of adequate duration.(3,4) About one-third of patients do not achieve remission even after therapy with as many as four different antidepressant medications.4 To make matters worse, many of antidepressants are associated with side effects that limit their tolerability and reduce their compliance.(5)

American Psychiatric Association (APA) diagnoses MDD and depressive episodes based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) Criteria published in May 2013.**(Table 1)**(6) In this criteria, MDD is defined as having a minimum of 5 symptoms over a 2 week period affecting patient functioning. Of these symptoms one must be either depressed mood and/or loss of interest or pleasure. The other possible symptoms include change in weight or appetite, insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, impaired concentration or indecisiveness and thoughts of death or suicidal ideation or suicide attempt.

Conditions that may mimic or co-exist with MDD must be screened including substance abuse, medical illnesses, other psychiatric disorders and bereavement. Apart from MDD, patients may also have a depressive episode **(Table 2)**.(6) According to DSM-5, a major depressive episode (MDE) can be rated as mild, moderate, or severe.(6) Symptoms of a MDE include any combination of these: depressed mood, loss of interest and enjoyment in usual activities, reduced energy and decreased activity, reduced self-esteem and confidence, ideas of guilt and unworthiness, pessimistic thoughts, disturbed sleep, diminished appetite, or ideas of self-harm.(6)

Table 1. DSM-5 Criteria for MDD[6]

5 or more of 9 symptoms (including at least symptom 1. and/or 2.) in the same 2-week period; each of these symptoms represent a change from previous functioning
1. depressed mood* (subjective or observed) 2. loss of interest or pleasure 3. change in weight or appetite 4. insomnia or hypersomnia 5. psychomotor retardation or agitation (observed) 6. loss of energy or fatigue 7. worthlessness or guilt 8. impaired concentration or indecisiveness 9. thoughts of death or suicidal ideation or suicide attempt

* for children or adolescent, mood can be irritability

Table 2. DSM-5 Criteria for depressive episode[6]

A	B
1. depressed mood 2. loss of interest and enjoyment in usual activities 3. reduced energy and decreased activity	1. reduced self-esteem and confidence 2. ideas of guilt and unworthiness 3. pessimistic thoughts 4. disturbed sleep 5. diminished appetite 6. ideas of self-harm

Severity
Mild: >1 Column A + 1-2 Column B or 5-7 symptoms but mild severity and functional impairment
Moderate: >1 Column A + 2-3 Column B or 7-8 symptoms but moderate functional impairment
Severe: all 3 Column A plus >3 Column B or any of the following: severe functional impairment, psychotic symptoms, recent suicide attempt or specific suicide plan or intent

COGNITIVE FUNCTION IN MDD

The disconnection between 'remission' of symptoms in MDD and functional recovery indicates that the critical determinant of functional outcome in MDD may not be detected by a multidimensional measure of illness severity (eg. total depression symptom score).(7,8,9) It may be surmised that select domains (eg. cognitive function) may be more critical to patient-reported health outcomes than are measures of total depression symptom severity.(10) Patients who suffer from MDD often have dysfunction in certain cognitive domains, such as executive function, working memory, visuospatial short-term memory, immediate and delayed free recall, psychomotor speed and verbal learning.(11) Evidence obtained using objective cognitive testing suggests that the foregoing observed deficits in MDD are an early feature of the disorder and of a magnitude likely to be clinically relevant.(12)

Convergent evidence indicates that MDD is the leading cause of disability amongst patients in both developed and emerging economies.[13] The principal source of cost and illness-associated morbidity is due to a significant decrease in role-function amongst affected individuals.[14,15] Moreover, patients with MDD who are unemployed are more likely to exhibit decreases in cognitive performance.[16] Patients (aged 18-65 years old) experiencing a MDE, disturbances in measures of cognition accounted for a greater degree of variability in workplace performance than did total depression symptom severity.[17]

In the acute phase of MDD, reduced performance on cognitive testing has been well documented.[18,19,20] Cognitive dysfunction is identified as a transnosological domain critical to outcomes across disparate mental disorders including, but not limited to, schizophrenia, bipolar disorder, and autism.[21] There is not one consensually agreed upon vocabulary for cognitive function, however a proposed taxonomy of hot and cold cognition has clinical resonance as well as heuristic value.[22] Hot cognition is defined as cognitive functions that are emotionally valence (eg. catastrophic reactions to real and/or perceived slights, anhedonia, negativistic rumination, negative recall bias, and disproportionate attention to negative stimuli).[23] Cold cognition would include examples such as executive function, information processing speed, learning and memory, as well as attention/concentration[23] **(Table 3)**. Neurobiologically, a discrete separation of hot and cold cognition does not exist.[23] Social cognition involves aspects of theory of mind, metacognition and mentalization.[24] Social cognition interdigitates some aspects of both hot and cold cognition.[23] A robust body of literature has documented a negative cognitive emotional bias amongst adults with MDD towards negatively valenced facial pictures, providing an example of how hot cognitive dysfunction and social deficits may interact.[25,26] Several factors interfere with cognition in MDD such as clinical (melancholic or psychotic) features, age, age of onset, illness severity, medication and comorbid conditions.[27]

Table 3. A framework for cognitive function in major depressive disorder

Cognition	Examples
Hot cognition	Rumination Catastrophic Reactions Bias towards negative stimuli (internal/external) Anhedonia (eg. anticipatory anhedonia)
Cold cognition	Executive function Information processing speed Learning and memory Attention/ concentration
Social cognition	Theory of mind Mentalization

(adapted from McIntyre et al.)[23]

Disturbances in cognition (eg. diminished ability to think, concentrate, or make decisions) as well as psychomotor slowing are criterion items of a MDE according DSM-5.[28] The majority of individuals actively symptomatic during a MDE exhibit or complain of cognitive dysfunction.[17] It has also been reported that a substantial percentage of individuals exhibit measureable cognitive dysfunction despite being in 'remission'.[9,29] Upon resolution of an MDE, measures of information processing speed as well as learning and memory may significantly improve but continue to exhibit abnormalities.[30,31] Qualitative research indicates that patient-reported measures of quality of life (eg. vitality, vigor and positive mental health), phenomenon that are not synonymous with, but are related to, cognition, are prioritized as treatment objectives by patients over total symptomatic remission.[32,33] MDD does not decrease overall measures of intelligence, but does decrease cognitive performance across discrete measures, with effect sizes ranging from 0.2 to 0.8.[34] Approximately 25-50% of patients with MDD exhibit a deficit in one or more cognitive faculties of one standard deviation or more below normative values.[35]

It is not known whether the screening, measurement, and systematic evaluation of cognitive function improves outcome in MDD.[23] Well-known screening tools for dementing disorders (eg. Mini-Mental Status Exam (MMSE), Montreal Cognitive Assessment (MoCA)), are not sufficiently sensitive to detect cognitive dysfunction amongst younger populations with MDD.[17] Moreover, subjective baseline measures of cognitive dysfunction in MDD do not correlate with objective measures of cognitive function.[17] Active depressive symptoms appear to be more likely to affect subjective when compared to objective measures.[36] Currently no 'gold standard' to measure cognitive function exist and although conventional measures (eg. Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale, and Patient Health Questionnaire) contain 1-2 items pertaining to cognitive function, they are suboptimal as a measure of cognition.[23] They do not capture the complexity and circumstances in which cognition affects individuals in day-to-day life.[10] Moreover they are self-reported, which have been shown to have minimal correlation with objective measures of cognitive function.[37,38] Available cognitive measurement tools that have been employed as dependent measures in assessment studies and/or as primary outcome measures in interventional studies include, but are not limited to, the Digit Symbol Substitution Test (DSST), Rey-Auditory Berval Learning Test (RAVLT), Perceived Deficits Questionnaire (PDQ), and the Cognitive and Physical Functioning Questionnaire (CPFQ).[17] The only tool, to our knowledge, that has been developed to screen for cognitive dysfunction in MDD is the THINC-it tool (httyps://www.thinccognition.com/thinc-cognition-tool) which is currently being validated at the University of Toronto, Mood Disorders Psychopharmacology Unit, Brain and Cognition Discovery Foundation.[10]

Cognitive dysfunction is present during the first episode of depression and in recurrent depression, as well as in late-life depression.[12,39,40] There are significant differences already visible from the second episode of MDD with memory, verbal fluency and frontal functions reduced.[41] There is also evidence to suggest that cognition in patients with recurrent depression further deteriorates with each major depressive episode (MDE).[42] Some patients show evidence of dysfunction even after remission of the MDE has been achieved.[43] Moreover, it has been observed that cognitive dysfunction not only persists despite amelioration of depressive symptoms but also may progress in subsets of individuals with MDD.[17] It has been shown that baseline measures of cognitive function amongst inpatients with MDD predict functional outcomes 6 months post discharge.[9,44] Individuals with minimal cognitive improvement have the lowest probability of psychosocial readjustment.[9] Individuals with MDD often receive pharmacotherapeutic interventions that may adversely affect measures of cognitive function.[10] For example, antipsychotic agents, benzodiazepines, hypnotics, antihistamine agents, are known to exert negative effects on measures of cognitive function.[45] Evidence indicates that deficits in cognitive function are more critical to patient-reported outcomes, including workplace disability, providing the basis for hypothesizing that treatments that are differentially effective on measures of cognitive function may be preferable and more acceptable to patients and more likely to improve measures of health outcome.[7]

Table 4. Comparison of Guidelines for MDD

	American Psychiatric Association (APA)	Canadian Psychiatric Association (CPA)	The National Institute of Health and Care Excellence (NICE)
Depressive episode-acute treatment	SSRI/SNRI/Bupropion/Mirtazapine	Venlafaxine/SSRIs/novel antidepressants	SSRIs/SNRIs
Prophylaxis of recurrent depressive disorder	To continue same antidepressant as acute treatment	To continue same antidepressant as acute treatment	To continue same antidepressant as acute treatment
Duration	Acute: 6-12 weeks Continuation: 6-9 months Maintenance: 1-2 years to lifetime	Acute: 8-12 weeks Continuation: 4-6 months Maintenance: 1-2 years to lifetime	No mention of duration for acute episode. Long term treatment for at least 2 years after an episode and up to 5 years in case of other risk factors
Psychosocial management	CBT/IPT	Psychoeducation +CBT/IPT	CBT/IPT (16-20 sessions)

SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin Norepinephrine Reuptake Inhibitor; MAOIs: Monoamine Oxidase Inhibitors; CBT: Cognitive behavioural therapy; IPT: Interpersonal therapy

(adapted from Saddichha S et al.)[46]

TREATMENT OF MDD

The desired outcome for MDD is to reduce the present symptoms of acute depression and help the patient return to original functional state before the onset of illness and to prevent further episodes. There are three phases of treatment for MDD: acute phase, continuation phase, maintenance phase. In different guidelines, slightly different recommendations have been made **(Table 4)**.[47] There is currently no one guideline used throughout Hong Kong. In the acute phase, the treatment goal is to attain remission (absence of symptoms) in a 6-12 week period. Followed by the continuation phase where the treatment goal is to eliminate residual symptoms or prevent relapse (return of symptoms within 6 months of remission) for the next 6-9 months. Then for the maintenance phase, to prevent recurrence of a separate depressive episode, lasting for 1-2 years. Some patients with greater risk for recurrence will require lifelong maintenance.[6]

When choosing a treatment it is important to be sensitive to the patient's concerns. It requires building therapeutic rapport and developing an alliance with the patient. Open discussion to educate the patient about their treatment provides an empathetic and trusting environment for the patient to feel comfortable in expressing their concerns.

PHARMACOLOGICAL THERAPY

The efficacy of SSRIs has been shown to be superior to placebo and comparable to other classes of antidepressants.[48,49] They are usually used as first-line therapy due to the fact that they are relatively well tolerated with fewer side effects and are relatively safe in overdose.[49] Some examples include fluoxetine, citalopram, sertraline, paroxetine, escitalopram and fluvoxamine. SSRIs have low affinity for histaminergic, s_1-adrenergic, and muscarinic receptors producing less anticholinergic and cardiovascular side effects than tricyclic antidepressants (TCAs) and are not associated with significant weight gain.[50-53] The most common adverse effects, which generally are mild and short lived, are gastrointestinal symptoms (i.e., nausea, vomiting, and diarrhea), sexual dysfunction in both males and females, headache, and insomnia.[51] If the SSRIs are discontinued, a step down process is warranted due to possible withdrawal symptoms.

Vortioxetine is a newer SSRI that has been shown in clinical trials to be effective in improving cognitive function and all symptoms of depression as assessed by Montgomery-Asterg Depression Rating Scale (MADRS).[54] Depression is associated with deficits in cognitive function and the Diagnostic and Statistical Manual 5 (DSM-5) lists impairment in cognition as a criterion item in the diagnosis of a major depressive episode.[54] MADRS is used to measure severity of depression and includes items such as apparent sadness, concentration difficulties, reported sadness, lassitude, inner tension, inability to feel, reduced sleep, pessimistic thoughts, reduced appetite, and suicidal thought.[54] Vortioxetine's mechanism of action is hypothesized to occur via the combination of a direct effect on the serotonin (5 HT) receptor activity and serotonin reuptake inhibition[55,56] **(Figure 1)**. In vitro studies in combinant cell lines show that vortioxetine is a 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and a 5-HT transporter inhibitor.[55,56] Vortioxetine has demonstrated improvements in executive function, acquisition of memory and recall, attention and concentration, as well as processing speed.[10]

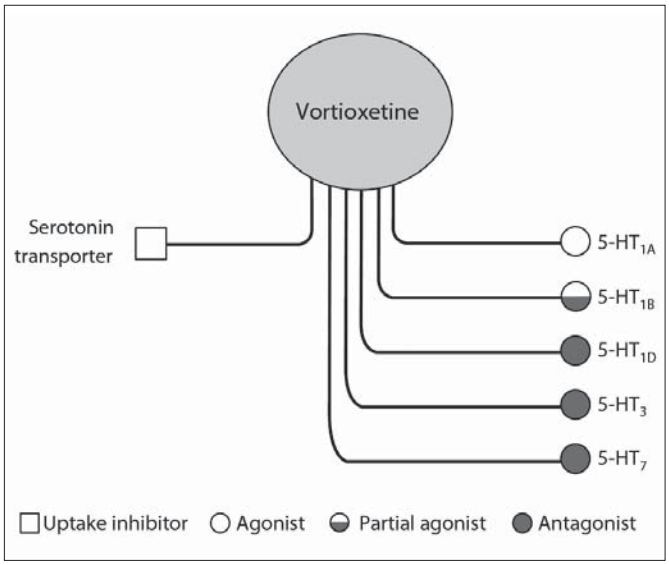

Figure 1. Pharmacologic Profile of Vortioxetine *(adapted from Schatzberg et al.)*[57]

In 11 different randomized, double-blind, placebo controlled trials of six or eight weeks' treatment duration, vortioxetine was efficacious and safe.[58] Across the 11 studies, 1824 patients were treated with placebo and 2204 with vortioxetine (5mg/day (N=1001); 10mg/day (N=1042); 15mg/day (N=449); 20mg/day (N=812).[58] The meta-analysis demonstrated that vortioxetine 5, 10 and 20mg/day compare to placebo were associated with significant reductions in MADRS total score with a significant p-value.[58] However 15mg/day was not significantly different from placebo. Vortioxetine 10 and 20mg/day were associated with significant reductions in 10 of 10 MADRS single-item scores[58] **(Table 5) (Table 6)**.

Table 5. Summary Characteristics of the 11 short-term, placebo-controlled studies of vortioxetine in patients with MDD

Study	Treatment period (weeks)	Dose per day (na)	Key inclusion criteria for MDD	Primary efficacy endpoint
NCT00839423[59]	6	Vortioxetine 5mg (108) Vortioxetine 10mg (100) Venlafaxine 225mg (112) Placebo (105)	MADRS ≥ 30	MADRS
NCT00635219[60]	8	Vortioxetine 2.5mg (155) Vortioxetine 5mg (155) Vortioxetine 10mg (151) Duloxetine 60mg (149) Placebo (145)	MDE ≥ 3 months and <12 months MADRS ≥ 26 MDE ≥ 3 months	MADRS
NCT00735709[61]	8	Vortioxetine 1mg (124) Vortioxetine 5mg (129) Vortioxetine10mg (122) Placebo (128)	MADRS ≥ 26 MDE ≥ 3 months	HAM-D_{24}
NCT01140906[62]	8	Vortioxetine 15mg (149) Vortioxetine 20mg (151) Duloxetine 60mg (146) Placebo (158)	MADRS ≥ 26 CFI-S ≥ 4 MDE > 3 months recurrent	MADRS
NCT01153009[63]	8	Vortioxetine 15mg (145) Vortioxetine 20mg (147) Duloxetine 60mg (146) Placebo (153)	MADRS ≥ 26 CGI-S ≥4 MDE ≥ 3 months recurrent	MADRS
NCT01163266[64]	8	Vortioxetine 10mg (154) Vortioxetine 20mg (150) Placebo (155)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months recurrent	MADRS
NCT01422213[54]	8	Vortioxetine 10mg (193) Vortioxetine 20mg (204) Placebo (194)	MADRS ≥ 26 MDE ≥ 3 months recurrent	DSST and RAVLT composite
NCT01255787[65]	8	Vortioxetine 5mg (142) Vortioxetine 10mg (147) Vortioxetine 20mg (149) Placebo (150)	MADRS ≥2 6 CGI-S ≥ 4 MDE ≥ 3 months	MADRS
NCT00672958[66]	6	Vortioxetine 5mg (292) Placebo (286)	MADRS ≥ 30 MDE ≥ 3 months	HAM-D_{24}
NCT00672620[67]	8	Vortioxetine 2.5mg (146) Vortioxetine 5mg (153) Duloxetine 60mg (149) Placebo (149)	MADRS ≥ 2 MDE ≥ 3 months	HAM-D_{24}
NCT01179516[68]	8	Vortioxetine 10mg (143) Vortioxetine 15mg (142) Placebo (149)	MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months recurrent	MADRS

CGI-S: Clinical Global Impressions Severity of Illness; DSST: Digit Symbol Substitution Test; HAM-D_{24}: Hamilton Anxiety Rating Scale-24 item; MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; RAVLT: Rey Auditory Verbal Learning Test; n[a] represents all randomized participants who took at least one dose of study medication and had a least one valid post-baseline measurement of the primary efficacy variable

(adapted from Thase et. al.)[58]

Table 6. Summary of demographics, baseline characteristics, and baseline efficacy parameters for patients included in the meta-analysis of 11 short-term, placebo-controlled clinical studies of vortioxetine in patients with MDD

	Placebo (N=1784)	Vortioxetine 5mg (N=989)	Vortioxetine 10mg (N=1028)	Vortioxetine 15mg (N=436)	Vortioxetine 20mg (N=800)
Age, years, mean (SD)	44.0 (12.46)	44.1 (12.79)	44.9 (12.24)	44.9 (13.61)	44.7 (12.49)
Sex, female, n (%)	1146 (64.2)	644 (65.1)	696 (67.7)	300 (68.8)	528 (66.0)
Race, n (%)					
Caucasian[a]	1451 (81.5)	752 (76.0)	812 (79.0)	360 (82.6)	648 (81.0)
Black	216 (12.1)	122 (12.3)	90 (8.8)	68 (15.6)	89 (11.1)
Asian	107 (6.0)	110 (11.1)	112 (10.9)	6 (1.4)	53 (6.6)
Other[b]	7 (0.4)	5 (0.5)	14 (1.4)	2 (0.5)	10 (1.3)
Mean duration of current MDE, n (%)					
<24 weeks	855 (47.6)	494 (49.9)	565 (55.0)	194 (44.5)	377 (47.1)
≥24 weeks	929 (52.1)	495 (50.1)	459 (44.6)	242 (55.5)	423 (52.9)
Number of previous MDEs					
N	1613	802	914	436	753
Mean (SD)	2.7 (2.24)	2.8 (3.05)	2.6 (2.12)	2.7 (1.90)	2.7 (2.30)
MADRS total score Mean (SD)	32.1 (4.00)	32.4 (4.04)	32.3 (4.03)	32.5 (4.09)	31.8 (3.88)
CGI-S total score Mean (SD)	4.7 (0.68)	4.8 (0.70)	4.7 (0.67)	4.7 (0.61)	4.6 (0.62)
HAM-A total score[c] Mean (SD)	19.7 (6.32)	20.1 (6.23)	20.6 (6.46)	19.4 (6.11)	18.9 (6.12)

CGI-S: Clinical Global Impressions-Severity of Illness; HAM-A: Hamilton Anxiety Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode
[a] Caucasian (or white, including Hispanic)
[b] Other: including American Indian/ Alaska Native, Native Hawaiian (or other Pacific Islander), and missing
[c] Study NCT01422213 did not measure HAM-A as an outcome measure; there, n-values of the HAM-A analysis set are 1586 (placebo), 983 (vortioxetine 5mg), 830 (10mg), 436 (15mg), and 596 (20mg)

(adapted from Thase et. al.)[58]

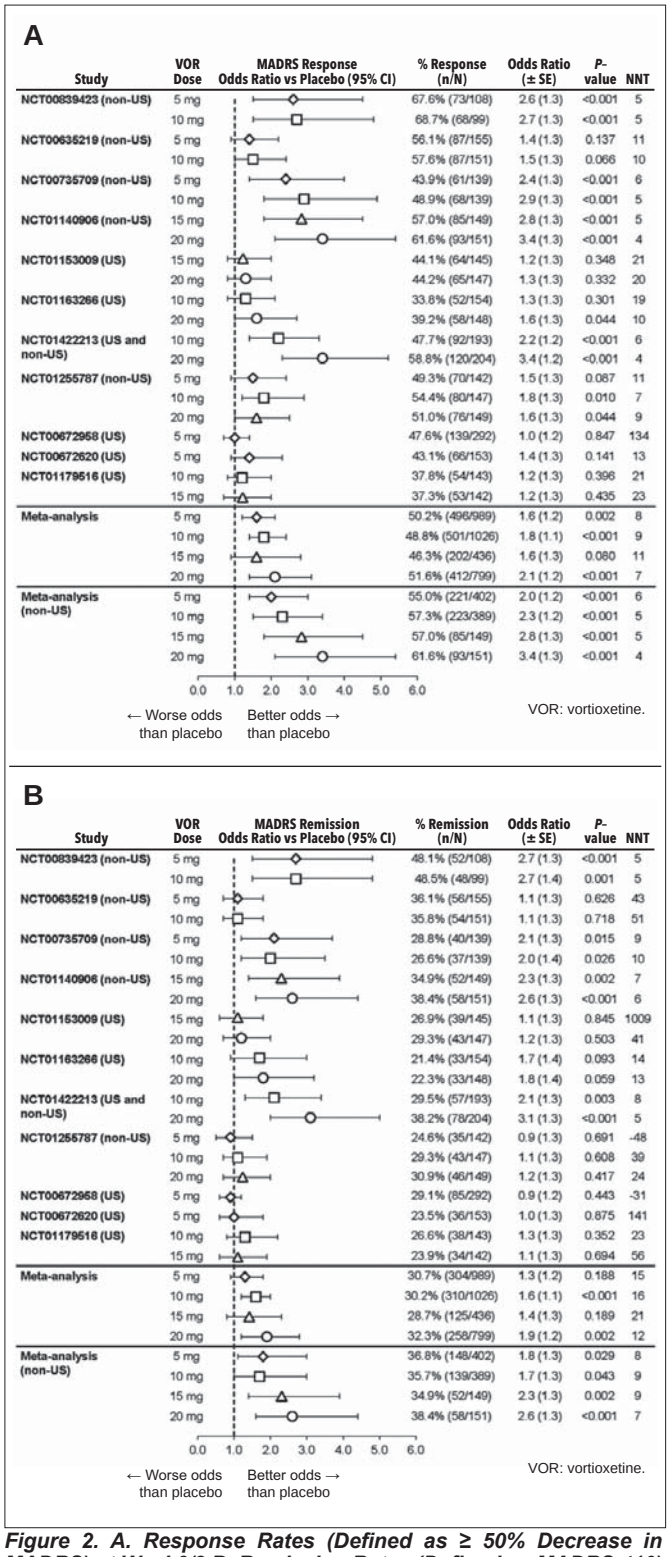

Figure 2. A. Response Rates (Defined as ≥ 50% Decrease in MADRS) at Week6/8 B. Remission Rates (Defined as MADRS ≤10) at Week 6/8 *(adapted from Thase et. al.)*[58]

The most common adverse reactions associated with vortioxetine include nausea, constipation and vomiting. Vortioxetine is weight-neutral and not associated with sleep disturbance with short-term (6-8 weeks) and long-term (up to 64 weeks) treatment as compared to placebo.[69-72] Treatment-emergent sexual dysfunction remains at placebo level during short- and long-term treatment.[72] No clinically significant effect on hepatic or renal assessments, heart rate, blood pressure or ECG parameters including QT, QTc, PR and QRS intervals were observed.[72]

When vortioxetine is compared with other antidepressant medications, it had a statistically significant higher remission rate than agomelatine and numerically higher remission rates than sertraline, venlafaxine and buproprion.[73] Withdrawal rates due to adverse effects were statistically significantly lower for vortioxetine than sertraline, venlafaxine and bupropion sustained release.[73] For patients not responding or tolerating prior SSRI or Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) therapy, vortioxetine may be a good alternative **(Figure 2)**.

In a different meta-analysis that identified nine placebo-controlled trials assessing cognitive effects of antidepressants, there was a small positive effect, however it was statistically insignificant.[74] Vortioxetine appeared to have the largest effect size on psychomotor speed, executive control and cognitive control; whereas duloxetine had the greatest effect on delayed recall.[74]

Tricyclic Antidepressants (TCAs) block the reuptake of norepinephrine (NE) and serotonin (5-HT) increasing their activities. They can also affect cholinergic receptors and also the neurologic and cardiovascular system, therefore causing adverse events.[75] Unwanted anticholinergic side effects include dry mouth, constipation, blurred vision, urinary retention, dizziness, tachycardia, memory impairment and delirium.[77] Due to TCAs affinity for adrenergic receptors, orthostatic hypotension is common.[78] TCAs can also produce severe arrhythmias, weight gain and sexual dysfunction.[78] TCAs have been linked to worse performance in executive function possibly due to its anticholinergic effects[79] **(Table 7)**.

At low doses venlafaxine inhibits 5-HT reuptake and has additional NE reuptake at higher doses.[80] Duloxetine inhibits 5- HT and NE reuptake across all doses.[80] The side effects of venlafaxine are similar to SSRIs and include nausea and sexual dysfunction and may be dose related.[80] Venlafaxine can also cause a dose-related increase in diastolic blood pressure, therefore blood pressure needs to be monitored regularly.[80] The most common side effects of duloxetine are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.[81]

Duloxetine is hypothesized to improve measures of cognitive function, principally through its effect on central norepinephrine signaling.[71,81,82] It has exhibited beneficial effects on measures of acquisition of memory, while replicated evidence indicates that it does not demonstrate effects on measures of executive function, attention, and concentration or processing speed.[74] In a small study evaluating the effects of escitalopram(n=36) compared with duloxetine (n=37) in adults with MDD over 24 weeks, the authors determined both treatments improved working memory as well as attention and disparate measures of executive function.[83] There is an absence of placebo in this underpowered study which disallows conclusions about the direct effects of SSRIs and SNRIs on cognitive function.[84] Another randomized, double-blind study involving duloxetine (60mg/day; n=207) and placebo (n=104) measuring cognition were evaluated in non-demented adults for 8 weeks.[81] The primary efficacy outcome was a composite neurocognitive metric comprising verbal learning and recall, digit-symbol substitution test (DSST), two-digit cancellation test, and letter-number sequencing.[81] Duloxetine significantly improved cognitive performance when compared with placebo in all subjects, mainly in verbal learning and memory.[81]

Another SNRI, Reboxetine (n=25) was compared with paroxetine (n=23) and placebo (n=26) on measures of cognitive function in adults aged 18-65 years with MDD over a period of 8 weeks. No significant differences were observed at endpoint for reboxetine or paroxetine treatment on the combined speed factor.[10]

Mirtazapine blocks the central presynaptic α_2-adrenergic receptors to increase NE and 5-HT.[52] It also blocks 5-HT_2, 5-HT_3 receptors and histamine receptors leading to less anxiety and less gastrointestinal side effects but more sedation.[52] Other side effects of mirtazapine include somnolence, weight gain, dry mouth and constipation.[52] There is increased noradrenergic transmission as the dose increases, so side effects such as weight gain is less with larger doses.[52] There is currently no evidence to support that mirtazapine can improve cognitive function in MDD patients.

Trazodone and nefazodone belong to the class of traizolopyridines. They have actions on serotonergic neurons inhibiting 5-HT_2 and the reuptake of 5-HT and enhancing 5-HT_{1A}.[76] Trazodone also blocks a_1-adrenergic and histaminergic receptors, which causes the side effects dizziness and cognitive slowing.[76] A rare but serious adverse effect of trazodone is priapism occurring in 1 in 6000 males.[76] Both medications can cause orthostatic hypotension. Nefazodone's limitation is hepatotoxicity which is a FDA black box warning.[76] Other side effects of nefazodone include dizziness, somnolence, dry mouth, nausea and asthenia.[76] There is currently no evidence to support that traizolopyridines can improve cognitive function in MDD patients.

Bupropion's mechanism of action is quite unique in that it acts on norepinephrine and dopamine reuptake pumps.[85] Adverse effects include nausea, vomiting, tremor, insomnia, dry mouth, skin reactions and agitation.[85] In patients with a history of predisposing factors to seizures (eg. CNS tumour), bupropion may cause dose-related increased risk of seizure recurrence.[86] A contraindication for bupropion is patients with eating disorders as they are more prone to electrolyte imbalances increasing risk of seizure.[86] At daily doses of 450 mg (the FDA-approved maximum dose) or less, the incidence of seizures is 0.4%.[86] There is currently no evidence to support that bupropion can improve cognitive function in MDD patients.

Monoamine Oxidase Inhibitors (MAOIs) work within the neuronal synapse inhibiting MAO enzyme to increase norepinephrine, 5-HT and dopamine. Non-selective MAO-A and MAO-B inhibitors include phenelzine, tranylcypromine and selegiline.[75] Selegiline is available as a transdermal patch acting directly in the brain. During longer durations of therapy with MAOIs, there is a down regulation of receptors resulting in a possible loss of effectiveness.[75] A selective and reversible inhibitor of monoamine oxidase type A, moclobemide, may have beneficial effects on cognitive function.[87] Moclobemide treatment in patients with vascular depression resulted in improved performance in neuropsychological tests except in the trail making test (TMT) B test which assesses visuospatial functions of memory suggestive of some activity in improving some cognitive domains.[87]

Most commonly, postural hypotension is an adverse effect of MAOIs which can be reduced if doses are divided throughout the day. Other adverse effects include weight gain, sexual dysfunction, fever, myoclonic jerking and deep tendon reflexes.[88] Phenelzine can be sedating whereas, tranylcypromine can act as a stimulant cause insomnia. When taking MAOIs, patients must avoid food with tyramine (eg. cheese, beer, fermented food, liver etc.) and beware of the symptoms of hypertensive crisis (occipital headache, stiff neck, nausea, vomiting, sweating, sharply elevated blood pressure.[88]

Table 7. Classes, Side effects and Considerations for antidepressant medications

Drugs	Drugs	Side Effects	Considerations
TCA	Imipramine Amitriptyline Doxepin Desipramine Nortriptyline	weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia	increased anticholinergic and cardiotoxic side effects; executive function may be worst due to anticholinergic effects
MAOI	phenelzine selegiline moclobemide	weight gain, fatigue, sexual dysfunction, hypotension	severe side effects including serotonin syndrome and hypertensive crisis; moclobemide may have some beneficial effects on cognitive function
SSRI	Fluoxetine paroxetine sertraline citalopram escitalopram vortioxetine	headaches, gastrointestinal distress, insomnia, fatigue, anxiety, sexual dysfunction, weight gain	first line treatment due to safer side effect profile; subtle side effect differences among class; vortioxetine has shown benefits for cognitive function and has an improved side effect profile
SNRI	venlafaxine duloxetine reboxetine paroxetine	nausea, insomnia, dry mouth, headache, increased blood pressure, sexual dysfunction, weight gain	slightly more frequent side effects than SSRI; duloxetine has benefits on memory and verbal learning
Atypical	buproprion	headache, agitation, insomnia, loss of appetite, weight loss, sweating	increased seizure risk for patients with eating disorders or epilepsy; no sexual dysfunction or weight gain; may help with quitting smoking.
	mirtazapine	sedation, increased appetite, weight gain	less sedation with higher doses; less nausea and sexual dysfunction than SSRI and SNRI; possible decrease in white blood cell counts
	trazodone	sedation, nausea, priapism (rare)	lower risk of weight gain and sexual dysfunction but may cause priapism; induces sleep as a positive effect

(adapted from Santarsieri et al.)[88]

In regards to the use of folic acid and vitamin b in depression, findings of low red cell folate and low vitamin B12 status has been noted in patients with MDD.[89] It is interesting to note that in Hong Kong, traditional Chinese diets are rich in folate and patients with high serum folate concentrations also can have MDD.[89] Low folate levels are furthermore linked to poor response to antidepressants. Folate and Vitamin B12 are major determinants of one-carbon metabolism in which S-adenosylmethionin (SAM) is formed.[90] SAM donates methyl groups crucial for neurological function.[90] A marker for folate and vitamin B12 deficiency is increased plasma levels of homocysteine.[90] One study suggests oral doses of folic acid (800 micrograms daily) and vitamin B12 (1mg daily) to try to improve the treatment outcome of MDD.[89] However, there are currently no studies that support the supplementation Vitamin B to improve cognitive function in depressed patients.

Many patients may look more natural remedies. The efficacy of St. John's Wort has mixed results when compared to placebo and other antidepressants.[90] The source of St. John's Wort may be variable and it can be bought over-the-counter. St. John's Wort interacts with many commonly used medications.[90] It is not generally recommended for use and currently there is no evidence of its efficacy to improve cognitive function.

Disparate pharmacotherapies have been minimally evaluated for their direct effects on cognitive measures in adults with MDD.[10] An example would be psychostimulants, which have mixed results on measures of total depression symptom severity in MDD, may have some benefit on self-reported measures of executive function.[91,92] Other treatments that are stimulant like (eg. Modafinil) have demonstrated improvements in cognitive functions in healthy controls, but have not been sufficiently studied in patients with MDD.[93] There are other potential therapeutic targets for the treatment of cognitive dysfunction in MDD. Lisdexamfetamine dimesylate (LDX) is a D-amphetamine prodrug that enhances the efflux of dopamine and norepinephrine in the central nervous system.[91] A randomized control trial (N=143) found that augmentation with LDX was efficacious in reducing self-reported executive dysfunction among participants with MDD with residual depressive symptoms.[39] It exerts pro-cognitive effects on learning and memory.[10] Erythropoietin (EPO) crosses the blood brain barrier and exerts an antidepressant-like and neuroprotective effect enhancing hippocampus-dependent memory and neuroplasticity, partly via the increased production of brain-derived neurotrophic factor (BDNF).[94] EPO improved verbal learning and memory in a preliminary randomized control trial involving participants with treatment resistant MDD involving 40 participants.[95] S-adenosyl methionine (SAMe) donates an essential methyl group to assist the synthesis of several neurotransmitters and glutathione.[96] A post-hoc analysis of a preliminary randomised control trial involving SSRI-resistant participants (N=40) with MDD found SAMe to improve in self-rated recall and word finding difficulties compared to placebo.[96] It is not known whether anti-inflammatory interventions or complementary alternative medications (eg. Omega-3 fatty acids) could exert a separate and independent effect on cognitive function.[10] There is a known relationship between innate immune systems and cognitive/emotional processing, which suggests that this category of treatment may benefit cognitive function.[97]

NON-PHARMACOLOGICAL THERAPY

Apart from pharmacological therapy, there are non-pharmacological treatments for MDD as well. Additional interventions with cognitive benefits in MDD may include, but are not limited to, cognitive remediation, aerobic exercise, as well as manual-based psychotherapies (eg. CBT).[10] Psychotherapy alone is only recommended for first-line therapy if the depressive episode is mild to moderate. Psychotherapy can be combined with pharmacological therapies for additive effects. Usually if recurrence occurs, psychotherapy would not be used alone. There is limited data but cognitive behavioural therapy (CBT) is equally effective as psychotherapy.[41] Despite unequivocal evidence indicating cognitive-emotional processing, it remains unclear the extent to which CBT improves measures of cold cognitive function. Neuromodulatory procedures other than ECT are more acceptable to patients suffering from MDD. Electroconvulsive therapy (ECT) is a safe and effective treatment for MDD when a rapid response is needed, risks of other treatments outweigh potential benefits, there is a history of poor response to antidepressants and a history of good response to ECT.[47] Usually ECT is for a total of 6-12 courses and a maintenance antidepressant is prescribed for the maintenance phase as relapse rate for ECT alone is high.[98,99] ECT has well established adverse effects on autobiographical memory, however the totality of evidence indicates that ECT exerts beneficial effects on measures of cognitive performance in adults with MDD.[23] Deep brain stimulation (DBS) has preliminary evidence to show that it may also have beneficial effects on cognition.[100] Transcranial magnetic stimulation (TMS), or light therapy may also be another alternative as an additive to pharmacological therapies.[101]

SPECIAL POPULATIONS

Depression amongst the elderly population is a problem that should not be overlooked and proper investigations should be carried out to rule out other possible disorders such as dementia. It is possible too for under treatment and over treatment in this population. Elderly people are more likely than younger people to develop cognitive impairments associated with medication use, possibly due to poorer renal and liver functions.[102] Some medications that can cause acute and/or chronic cognitive impairment in elderly include anticholinergic medications, benzodiazepines, opioid analgesics, antipsychotics, anti-parkinsonian drugs, antidepressants, anticonvulsants, antibiotics, histamine-1 receptor antagonists, histamine-2 receptor antagonists, corticosteroids, NSAIDS (nonsteroidal anti-inflammatory agent), and cardiac medications[102,103] **(Table 8)**. Early diagnosis and withdrawal of the offending agent are essential for the prevention of drug-induced dementia and delirium and prescribers should take care to 'start low and go slow'.[102] The risk of drug induced confusion increases with the number of drugs prescribed.[104]

In the elderly population, SSRIs are the first choice for treatment of MDD due to a favourable side effect profile.[105] Bupropion and venlafaxine are often selected because of milder anticholinergic and less frequent cardiovascular side effects.[105] The efficacy of vortioxetine for the treatment of MDD in the elderly (aged 64-88) was demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study.[72] No dosage adjustment for vortioxetine is recommended on the basis of age.[72] It has also been shown that vortioxetine (10 and 20mg/day) significantly improves cognitive performance in patients with MDD across several domains, including executive function, attention/speed of processing, and memory.[71]

In Paediatrics, it is not uncommon for children to have depression. Some nonspecific symptoms for this population include boredom, anxiety, failing adjustment and sleep disturbance.[106] Fluoxetine is FDA-approved for patients younger than 18 years of age. Sertraline has also been tried in this group of patients. Generally TCAs and several SSRIs are viable treatment options when monitored appropriately.[106] There are currently no antidepressants with cognitive function benefits approved for this group of patients.

Table 8. Drugs associated with cognitive impairment in the elderly

Drug Class	Example	Risk	Comment
Anticholinergics	Atropine Scopolamine	High	Glycopyrronium bromide is a safer agent for anaesthetic premedication
Benzodiazepines	Nitrazepam Flurazepam Diazepam	Medium-High	Cognitive impairment is more common with long-acting agents. Withdrawal delirium also occurs
Opioid analgesics	Pethidine	High	Risk may be highest with pethidine
Antipsychotics	Chlorpromazine	Low-Medium	Although often used in treatment of delirium, antipsychotics with significant anticholinergic activity can worsen confusion
Anti-parkinsonian drugs	Bromocriptine Levodopa Selegiline	Medium-High	Risk is highest in drugs with anticholinergic activity
Antidepressants	Amitriptyline Imipramine Nortriptyline SSRIs	Medium-High	Risk is highest in drugs with anticholinergic activity
Anticonvulsants	Phenytoin	Low-Medium	Risk may be lowest with valproic acid and newer anticonvulsants
Histamine-1 Antagonist	Cimetidine Ranitidine	Low	Proton Pump Inhibitors are less likely to cause delirium
Histamine-2 Antagonist	Chlorphenamine	Low	Antihistamines are available in many over-the-counter preparations
Cardiovascular drugs	Quinidine Digoxin Methyldopa Beta-blockers Diuretics ACE inhibitors	Low-Medium	Digoxin toxicity is dose related, but in the elderly people confusion may occur with normal serum concentrations
Corticosteroids	Prednisolone	Medium	Risk is dose-related
NSAIDs	Indomethacin Ibuprofen	Low-Medium	Paracetamol is a safer alternative for short term use
Antibiotics	Cephalosporins Penicillin Quinolones	Low	Although delirium has been reported with many antibiotics, this may be more related to the effect of the underlying infection

(adapted from Moore, A. and O'Keeffe S.T.)[103]

Pregnant women have an increased risk of developing depressive illness and about 10-15% of them experience depression during pregnancy.[107] The risk of depression appears to be the highest in the second and third trimester and almost half of these women continue to have symptoms after the end of pregnancy.[108] It is important to treatment MDD during pregnancy as it has been associated with increased risk of complications during pregnancy, including increased risk of preeclampsia, preterm birth, abnormal bleeding, miscarriages and even fetal death.[109] The risks and benefits must be properly weighed out before treating a pregnant woman for depression.[107] Relapse rates are higher for non-treated depression during pregnancy.[110] When newly prescribing antidepressants to a woman of child-bearing age, it is important to educate the patient on risks, methods of prevention of pregnancy and to discuss planning pregnancy with their doctor. Sertraline and citalopram are first-line in treatment among SSRIs for depression in pregnancy.[110] Currently there is no known studies of antidepressants that improve cognition function shown to be safe to use in pregnant woman.

When considering breastfeeding, all antidepressants are present in human milk to some extent. Much of the current data are derived from case reports and not much evidence is available. An individualized risk-benefit analysis of treatments should be conducted. Data from a recent meta-analysis indicated that all antidepressants were detected in milk but that not all were found in infant serum.[111] Infant serum levels of nortriptyline, paroxetine and sertraline were undetectable in most cases, however serums levels of citalopram and fluoxetine exceeded the recommended 10% maternal level in 17% and 22% of cases, respectively.[112] Few adverse outcomes were reported for any of the antidepressants or conclusions could not be drawn due to an insufficient number of cases.[112] There is little or no evidence that ethnic or regional "medicines" are safe or effective, thus their use by healthcare providers is strongly cautioned.[112]

REFRACTORY PATIENTS

The most widely accepted definition for treatment-resistant depression (TRD) is patients who do not achieve remission after two optimal antidepressant trials and this makes up about 40% of patients with MDD.[113] The majority of treatment resistant patients are likely to be under treated and with the help of an augmenting agent or switch of medication, they may achieve remission. It is important to address other issues as well such as correct diagnosis, adequate dose and duration, patient adherence etc. Non-pharmacological therapies can be used additionally to pharmacological therapy and may be beneficial for refractory patients. Refractory depression is difficult to treat and outcomes are usually poor. A trial of the STAR-D program (Sequenced Treatment Alternatives to Relieve Depression) may help treatment.[113] Refractory depression is difficult to treat successfully and outcomes are poor especially if evidence based protocols are not followed.[113] The evidence base has been substantially improved by publication of results of the STAR-D program (Sequenced Treatment Alternatives to Relieve Depression).[113]

CONCLUSION

Choosing the right therapy for a patient through education and being sensitive to a patient's individual concerns is important. There are some therapies that may suit some patients but not others. It is important for healthcare providers to be empathetic and assertive. Cognitive function is a major part of MDD and it is important to address cognitive deficits. A patient's ability to return to work or daily functioning has a large impact on patient's health and on the economy. Many times, symptomatic remission does not mean functional recovery. A gold standard to assess cognitive function needs to be developed and more studies on antidepressants in regards to their effects to improve cognitive functioning must be done. Currently the SSRI vortioxetine has the most evidence in support of its cognitive function improving properties. Other therapies such as duloxetine may also improve certain cognitive domains. There are many postulated mechanisms to help improve cognitive function and different agents are being on trial. Special care needs to be taken in the elderly, paediatrics and pregnant or breastfeeding mothers.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Considering Cognitive Function Treatment in Major Depressive Disorder (MDD)

1. ***Which of the following is not a diagnostic criteria for Major Depressive Disorder as defined by DSM-5?***
   a) impaired concentration or indecisiveness
   b) psychomotor retardation or agitation (observed)
   c) loss of energy or fatigue
   d) thoughts of harming or inflicting pain onto others

2. ***With regard to SSRIs, which is correct?***
   a) usually used as first-line therapy
   b) relatively dangerous when overdose
   c) low affinity for histaminergic and muscarinic receptors producing more side effects compared to other treatment options
   d) all of the above

3. ***Which of the following are advantages of vortioxetine:***
   I. weight neutral
   II. sexual dysfunction
   III. improved cognitive functioning
   IV. no sleep disturbance

   a) III
   b) I, III & IV
   c) I & III
   d) I, II, III & IV

4. ***Which of the following is not an example of hot cognition?***
   a) attention, concentration
   b) rumination
   c) bias towards negative stimuli
   d) anhedonia

5. ***Patients who suffer from MDD often have dysfunction in certain cognitive domains which may include:***
   a) imagination
   b) visuospatial short-term memory
   c) long-term memory
   d) all of the above

6. ***Which of the following pharmacological agent is the most suitable choice for a paediatric patient suffering from MDD?***
   a) bupropion
   b) lithium
   c) mirtazapine
   d) fluoxetine

7. ***Which of the following medications have been associated with cognitive impairment in the elderly***
   I. Digoxin
   II. Ranitidine
   III. Bromocriptine
   IV. Chlorphenamine

   a) III
   b) II, IV
   c) I, III
   d) I, II, III, IV

8. ***In regards to the use of vortioxetine in the elderly, which of the following statements is true?***
   a) elderly should be started on a dosage of 15mg daily
   b) efficacy was demonstrated in a randomize, double-blind, placebo-controlled study in elderly (aged 64-88)
   c) elderly experience fewer side effects
   d) none of the above

9. ***Which of the following statements is true regarding treatment of pregnant woman for depression?***
   a) pregnant woman should not be treated for depression
   b) pregnant woman should get an abortion before commencing treatment
   c) sertraline and citalopram are first-line in treatment among SSRIs for depression
   d) TCAs are first-line in treatment for depression

10. ***In refractory patients, possible treatment options include:***
    I. trial of alternative medicines eg. Traditional Chinese Medicine, natural remedies
    II. stop all treatments and let the patient recover on their own
    III. switch medications to a different agent with different mechanism of action
    IV. augmentation of the current antidepressant

    a) I and III
    b) II
    c) III, IV
    d) I, II, III, IV

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 232(D&T)

An Overview of the Pharmaceutical Properties of Oral Care Products

1. D 2. D 3. B 4. C 5. D 6. B 7. A 8. D 9.B 10. D

Genvoya® Abbreviated Prescribing Information (Version: HK-OCT15-EU-OCT15) **Presentation:** Green, capsule-shaped, film-coated tablet, debossed with "GSI" on one side and "510" on the other side of tablet. immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir. food. Elderly: No dose adjustment is required. Renal impairment: No dose adjustment is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) in patients with estimated CrCl < 30 mL/min. Genvoya should be discontinued in patients with estimated CrCl that declines below 30 mL/min during treatment. (Child Pugh Class B) hepatic impairment. Genvoya has not been studied in patients with severe hepatic impairment (Child Pugh Class C); therefore, Genvoya is not recommended for use in patients with severe hepatic impairment. efficacy of Genvoya in children younger than 12 years of age, or weighing < 35 kg, have not yet been established. No data are available. contraception. Pregnancy: Genvoya should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. in humans. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients; Co- administration with the following medicinal products due to the potential for serious or life-threatening adverse reactions or loss of virologic response and possible resistance to Genvoya: alpha 1-adrenoreceptor antagonists: alfuzosin; antiarrhythmics: amiodarone, quinidine; anticonvulsants: carbamazepine, phenobarbital, phenytoin; antimycobacterials: rifampicin; ergot derivatives: dihydroergotamine, ergometrine, ergotamine; gastrointestinal motility agents: cisapride; herbal products: St. John's wort (Hypericum perforatum); HMG Co-A reductase inhibitors: lovastatin, simvastatin; neuroleptics: pimozide; PDE-5 inhibitors: sildenafil for the treatment of pulmonary arterial hypertension; sedatives/hypnotics: orally administered midazolam, triazolam. **Warnings and Precautions:** While effective viral suppression with antiretroviral therapy has been proven to substantially reduce risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines. Patients co-infected with HIV and hepatitis B or C virus: Discontinuation of Genvoya therapy in patients' co-infected with HIV and HBV may be associated with severe acute exacerbationsconducted. Liver disease: Safety and efficacy of Genvoya in patients with significant underlying liver disorders have not been established. Patients with pre-existing liver dysfunction, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. Blood lipids and glucose:demonstrated in vitro and in vivo to cause a variable degree of mitochondrial damage. Any child exposed in utero to nucleoside and nucleotide analogues, even HIV negative children, should have clinical and laboratory follow up and should be fully investigated for possible mitochondrial dysfunction in case of relevant signs or symptoms. Immune Reactivation Syndrome: In HIV infected patients treated with CART, immune reactivation syndrome has been reported. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation. complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases. advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement. exposure to low levels of tenofovir due to dosing with tenofovir alafenamide cannot be excluded. Co-administration of other medicinal products:with other antiretroviral medicinal products; Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 Qg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception. The effect of co-administration with oral contraceptives containing progestagens other than norgestimate is not known and, therefore, should be avoided; Genvoya contains lactose monohydrate, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take Genvoya. **Adverse reactions:** Diarrhea and headache. Autoimmune disorders (such as Graves' disease) have been reported. **Drug interactions:** Products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of HBV infectithe components of Genvoya and the following co-administered medicinal products: Antifungals (ketoconazole/ elvitegravir, itraconazole, voriconazole, posaconazole, fluconazole); Antimycobacterials (rifabutin/elvitegravir/cobicistat); Anti-hepatitis C virus medicinal products (telaprevir/elvitegravir /cobicistat, boceprevir); Macrolide antibiotics (clarithromycin, telithromycin); Anticonvulsants (carbamazepine/elvitegravir/cobicistat); Glucocorticoids: inhaled/nasal corticosteriods (fluticasone); Antacids (magnesium/ aluminium-containing antacid suspension/elvitegravir/ritonavir); Food supplements (mutivitamin supplements); Oral anti-diabetics (metformin); Oral contraceptives (norgestimate/ethinylestradiol/elvitegravir/ cobicistat); Antiarrhythmics (digoxin, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone); Anti-hypertensives (metoprolol, timolol, amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil); Endothelin receptor antagonists (bosentan); Anticoagulants (warfarin, dabigatran); Inhaled beta agonist (salmeterol); HMG CO-A reductase inhibitors (atorvastatin, pitavastatin, lovastatin, simvastatin); Phosphodiesterase type 5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil) Antidepressants (tricyclic antidepressants, trazodone, selective serotonin reuptake inhibitors, escitalopram); Immunosuppressants (ciclosporin, sirolimus, tacrolimus); Sedatives/hypnotics (buspirone, clorazepate, diazepam, estazolam, flurazepam, lorazepam, triazolam, zolpidem, orally administered midazolam/tenofovir alafenamide, intravenously administered midazolam/tenofovir alafenamide); Anti-gout (colchicine).

Before prescribing, please consult full prescribing information which is available upon request.

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Reference: 1. Genvoya Prescribing Information (Version: HK-OCT15-EU-OCT15)

Further information can be provided upon request.

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Chemical Constituents and Bioactivities of Rhododendri Daurici Folium

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Botanical Name: *Rhododendron dauricum* L.
Plant Family: *Ericaceae*
Chinese Name: 興安杜鵑（正名)；滿山紅，映山紅，迎山紅，山崩子，靠山紅（俗名)
Pharmacopoeia Name: Rhododendri Daurici Folium
Part Used: Dried leaf
Other name: Dahurian Rhododendron Leaf

ABSTRACT

Rhododendri Daurici Folium is the dried leaf of *Rhododendron dauricum* L which is widely distributed in Heilongjiang, inner Mongolia and Jilin. It is a herbal medicine with a long history for treating chronic and acute tracheitis and asthma. This herb is composed of a wide range of bioactive components providing useful biological effects but very few studies have reported on the relations between the bioactivities and therapeutic effect. Moreover, there are more than 400 species of *Rhododendron* found in China and there is little morphological difference between *Rhododendron dauricum* L. and its confusing species. To authenticate *Rhododendron dauricum* L. HPLC analysis should be conducted as well as morphological identification. This review aims to (1) compile the available information related to its therapeutic effect and (2) demonstrate the difference in chemical compositions between *Rhododendron dauricum* L. and its confusing species.

Keywords: *Rhododendri Daurici Folium, Rhododendron dauricum L., Rhododendron mucronulatum Turcz,, farrerol, anti-tussive, expectorant effects, bronchitis, asthma, pulmonary heart disease*

DESCRIPTION AND BACKGROUND

Rhododendri Daurici Folium, as shown in **Figure 1**, is the dried leaf of *Rhododendron dauricum* L (興安杜鵑). In China it is commonly called *Man Shan Hong* (滿山紅) owing to its red pedals. *Rhododendron dauricum* L is one of the species of *Rhododendron*. It is distributed mainly in Heilongjiang, Inner Mongolia, and Jilin Provinces in China as well as in Russia, Mongolia, the Korean Peninsula, Japan and Taiwan. It is a common shrub growing in Northeast in China and high latitude.[1] There are approximately 460 species of *Rhododendron* in China. Only *Rhododendron dauricum* L is endorsed for uses as a Chinese medicine according to 2015 edition of Chinese Pharmacopoeia (CP), which specifies that the content of farrerol should not be less than 0.08%(w/w).[2]

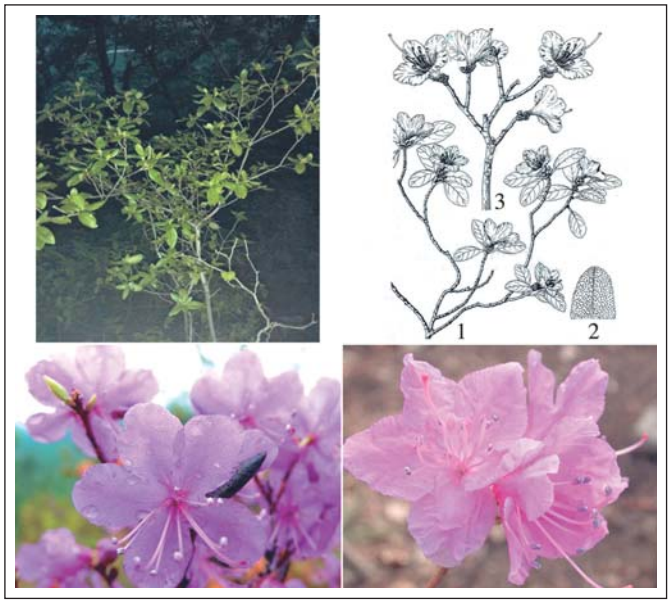

Figure 1. Photographs of Rhododendron dauricum L. *(Top left),* ***flowers of the herb*** *(Bottom left),* ***and flowers of Rhododendron mucronulatum Turcz, (bottom right)****. Sketches of these two plants are shown at top right-hand side; 1 = Rhododendron dauricum L, 2 = bottom feature of a leaf of R. Dauricum, and 3 = Rhododendron mucronulatum Turcz. (Photos of the flowers adopted from http://frps.eflora.cn/frps/Rhododendron%20dauricum and sketches adopted from http://frps.eflora.cn/frps/Rhododendron%20dauricum)*

Contraindications
Patients will a history of liver and heart ailments should avoid long-term use of this herb. Grayanotoxin I of Rhododendri Daurici Folium can cause decrease in heart rate and damage of liver tissues.

Undesirable Effect
Over-intake of volatile oils of Rhododendri Daurici Folium will cause symptoms of nausea, vomiting, dizziness, angina, sweating and asthenia.

Interaction with Conventional Drugs
No interaction with conventional drugs has been reported.

Morphological Features and Identification[1, 2, 6]

Rhododendron dauricum L is a semi-deciduous shrub. It is 0.5–2 m tall with numerous short and curved branches. The branches are dark-brown and covered with scales and villi. The scales are oval shape. Petiole is 2–6 mm long covered with villi. Leaf blade is papery to almost leathery, elliptic, ovate-lanceolate or triangular-ovate, with 1–5cm length and 1–1.5 cm width. The base of leaf blade is obtuse but the apex is acute and grown with mucronate. The margin of leaf blade is slightly revolute. The illuminated part of leaf is deep green with loosely-packed white glandular scales but the shaded part is pale green with densely-packed white glandular scales. The glandular scales are brown and different sizes. The inflorescence is usually 1-4 flowered and the flowers appear before the leave. The pedicel is 2-8 mm long and covered with scarly buds. The calyx is shorter than 1mm. It is 5-lobed and densely covered with scales. The corolla is funnelform with purplish-red petals. It is 1.3-2.3 cm long and covered with villi. 10 stamens with uneven length are found in each flower. The stamen is shorter than corolla. The anther is purplish-red. The filament is flat with villi at the base. 5 ovaries are found in each flower. The ovary is densely covered with scales. The style is smooth and purplish red. The capsule is ellipsoid-ovoid shape and with length 1-1.5 cm and diameter 5mm. The flowering season starts from May to June. The fruiting season is in July. *Rhododendron dauricum* L grows in acidic soil of open forests of submontane regions.

Comparison with Confusing Species

As mentioned before, there are approximately 460 species of *Rhododendron* in China. Many of them have purplish-red petals, and leathery and ovate-lanceolate leaves. Therefore, it is difficult to distinguish *Rhododendron dauricum* L from other confusing species merely by morphological comparison because there is no obvious morphological difference between *Rhododendron dauricum* L and other species **(Figure 1)**. However, the chemical compositions between them are different. Our preliminary works show that the HPLC chromatographic fingerprints between *Rhododendron dauricum* L **(Figure 2B)** and one of the confusing species, which is mostly likely *Rhododendron mucronulatum* Turcz, are significantly different. **(Figure 2C).** Amongst the four selected biomarkers monitored **(Figure 2A)**, the content of hyperoside, quercetin and farrerol in confusing species was much lower than that of *Rhododendron dauricum* L. But more importantly, farrerol content of the confusing species did not meet the limit of not less than 0.08% specified in the Chinese Pharmacopoeia (2015). In addition, the peak areas at RRT 1.099 and 1.173 were less but those in RRT 1.111 and 1.122; the latter two components were much higher in the confusing species. Because the chemical profiles of different *Rhododendron* species are significantly different, HPLC analysis should be used for identification of *Rhododendron dauricum* L along with morphological features. Nevertheless, further investigation is necessary in order to establish a full picture between *Rhododendron dauricum* L and other species of *Rhododendron*.

CHEMICAL CONSTITUENTS OF RHODODENDRI DAURICI FOLIUM

Rhododendri Daurici Folium is comprised a wide array of chemical constituents like flavonoids, terpenes and volatile oils,[4] in which flavonoids make up the largest proportion.

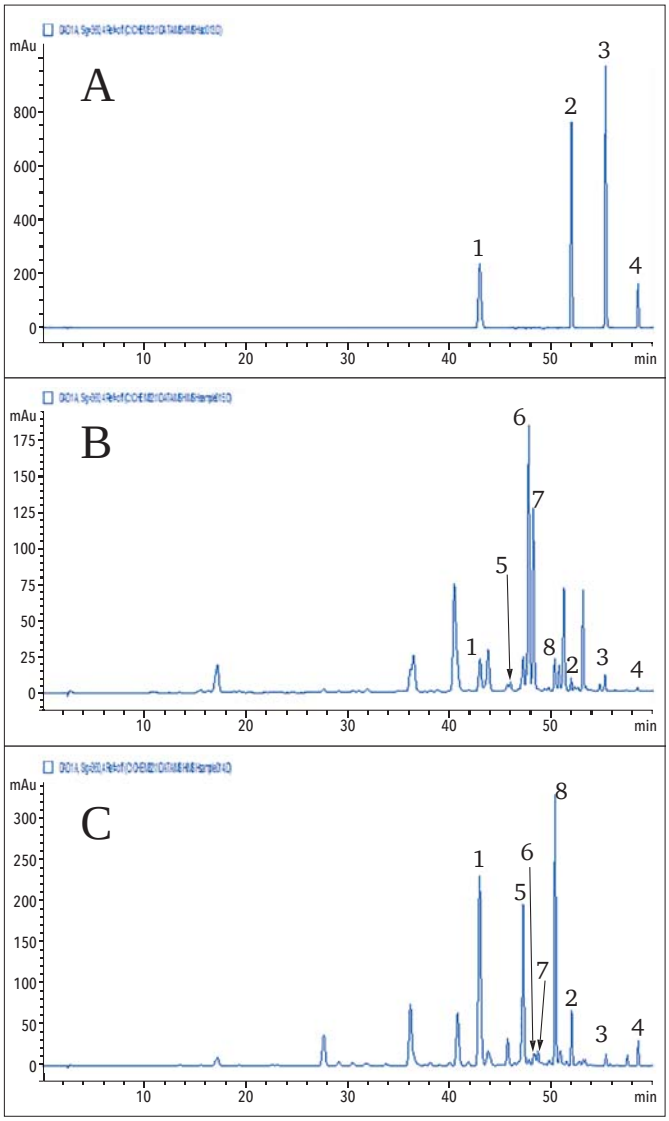

Figure 2. HPLC chromatographic fingerprints of Rhododendron species. *Chromatogram of selected biomarkers (A) ; Fringerprint of the leave extract of confusing species (B) and of Rhododendron dauricum L (C). Peak 1= hyperoside, 2= quercetin, 3= kaempferol, 4= farrerol, 5= peak with RRT 1.099, 6= RRT 1.111, 7= RRT 1.122, 8= RRT 1.173*

Several flavonoids, namely farrerol, flavonone, flavonol, flavone and flavonol glucoside , have been reported to be present in Rhododendri Daurici Folium. These flavonoids contribute to various biological activities (e.g. anti- inflammatory, anti-bacterial and antioxidant activity for scavenging free radicals).[5] Among those flavonoids, hyperoside, farrerol, quercetin and kaempferol, as shown in **Figure 3**, are reviewed and discussed in this article owing to their abundance and bioacitvity. *Rhododendri Daurici Folium* is often used to treat chronic and acute tracheitis and relieve asthma. Because of its low toxicity and therapeutic effects, it has been listed in the monograph of Chinese Pharmacopoeia.[3] Rhododendri Daurici Folium is acrid and bitter in taste. It is cold in nature.

BIOLOGICAL EFFECTS AND BIOACTIVITIES

Until now, more than 40 phytochemicals have been identified in Rhododendri Daurici Folium. They can be divided into flavonoids, terpenes, volatile oils and some other compounds. Among those components, the bioactivities of Rhododendri Daurici Folium are mainly attributed to the flavonoids. In this

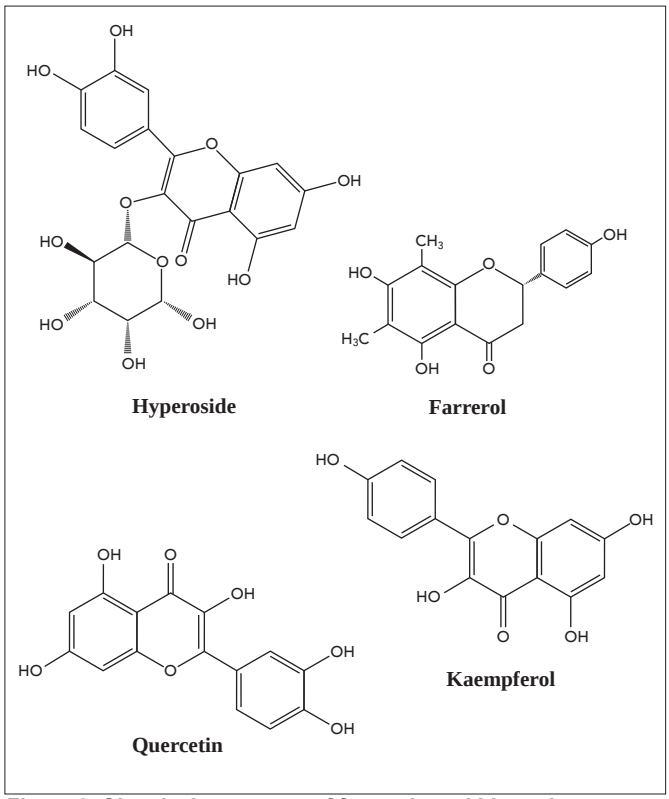

Figure 3. Chemical structures of four selected biomarkers.

article only hyperoside, farrerol, quercetin and kaempferol are reviewed and discussed in more details since separation and determination of bioactivities of these four constituents have been descripted in previous research while little has been mentioned on the study of other compounds. Hence, these four components are chosen as the selected biomarker for this herb.

1. Hyperoside

Hyperoside which is also called quercetin 3-O-b-d-galactoside is one of the most dominant constituents in Rhododendri Daurici Folium.[7] It is a potential drug to relieve asthma owing to its anti-inflammatory effect. Asthma is known as airway hyper-responsiveness and chronic airway inflammation. It is attributed to infiltration of inflammatory cells into lung tissues, overproduction of mucus, production of Immunoglobulin E (IgE), overexpression of Th2-mediated cytokines, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-4, IL-5 and IL-13 from mast cells. Also transcription factor NF-kB which regulates the expression of genes in response to infection, inflammation and other endogenous and exogenous stressors contribute to asthma. Hyperoside exhibits anti-inflammatory effect by decreasing the level of intracellular-calcium, decreasing the production and mRNA expression of TSLP, abrogating the NF-κB pathway and decreasing the mRNA expression of IL-1β and IL-6 in human mast cell line-1 (HMC-1 cells) as shown in **Figure 4**. TSLP directly interacts with mast cells this plays a role in the pathogenesis of allergic diseases. Its activation is regulated by the intracellular calcium in mast cells. Moreover, the nuclear translocation of NF-κB depends on phospholipase C-related calcium release and NF-κB is one of the most important regulators IL-1β and IL-6. Activation of NF-κB is involved in the pathogenesis of asthma. As a result, regulation of the level of intracellular-calcium, TSLP, NF-κB, IL-1β andIL-6 is important to relieve asthma.[8]

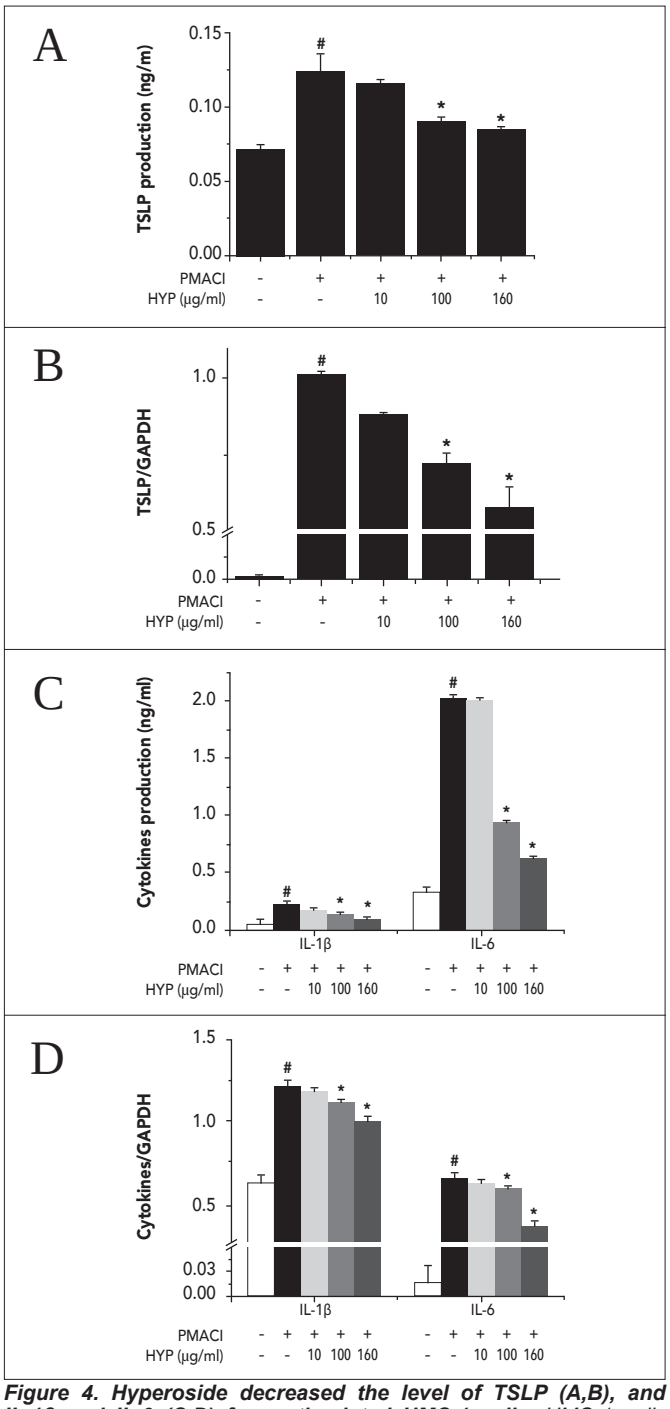

Figure 4. Hyperoside decreased the level of TSLP (A,B), and IL-1β and IL-6 (C,D) from stimulated HMC-1 cells. *HMC-1 cells were pretreated with HYP for 2 h. HMC-1 cells (4 × 105) pretreated with HYP were stimulated with restriction enzyme PMACI for 7 h. The production of TSLP was analyzed with ELISA.* ***(A)*** *The levels of mRNA expression were quantified by densitometry.* ***(B)*** *HMC-1 cells pretreated with HYP were stimulated with PMACI for 8 h. The production of IL-1β and IL-6 was analyzed with ELISA.* ***(C)*** *HMC-1 cells pretreated with HYP were stimulated with PMACI for 6 h. The mRNA expressions of IL-1β and IL-6 were analyzed with an RT-PCR analysis.* ***(D)*** *#p <0.05; significantly different from unstimulated cells. *p <0.05; significantly different from PMACI-stimulated cells.*[8]

2. Farrerol

Farrerol was found to be another major constituent in Rhododendri Daurici Folium. It constitutes to 0.08-0.15% of the herb.[11] Farrerol is proved to relieve asthma by inhibiting NF-kB activation induced by ovalbumin (OVA), reducing the total number of inflammatory cells, eosinophils, IL-4, IL-5 and IL-13 levels in lung tissues and OVA specific IgE levels in

serum as shown in **Figure 5**.[9] It is also a potential medicine for treating bacterial tracheitis owing to the anti-bacterial properties. It is proved to inhibit *Staphylococcus aureus* growth in bovines by regulating antimicrobial peptide expression by bovine mammary epithelial cells (bMEC) as shown in **Figure 6** after *S. aureus* invasion.[10] Bacterial tracheitis is mainly caused by *S. aureus*. Inhibiting the *S. aureus* growth will be effective in treating bacterial tracheitis.[11]

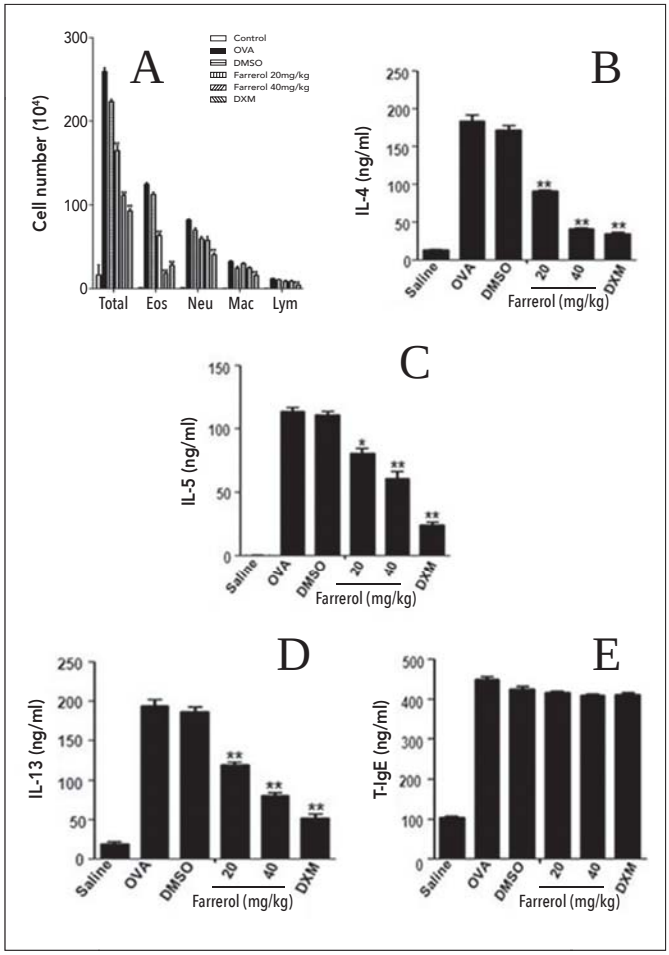

Figure 5. Effects of farrerol on OVA-induced inflammatory cell recruitment and mucus hyper-secretion and on cytokine (A) and chemokine levels in BALF and serum immunoglobulin production in vivo (B-E). *Inflammatory cell counts in BALF obtained from sensitized mice 24 h after the last farrerol treatment. Differential cell counts were identified eosinophil (Eos), macrophage (Mac), neutrophil (Neu) and lymphocyte (Lym)* ***(A)****. BALF and blood were collected and centrifuged 24 hours after the last OVA challenge (B-E). Results of IgE in serum were expressed as mean + SD with n = 10* ***(E)****. *p < 0.05, **p < 0.01 vs. OVA* ***(B-E)****.*[9]

3. Quercetin

Quercetin is rich in many fruits, vegetables and leaves, present as many different glycosidic forms. After ingestion, enzymes in the mouth and the intestines hydrolyze quercetin glycosides to quercetin aglycones. Its anti-inflammatory property contributes to treat asthma. It exerts the effect by suppressing Th2 cell differentiation, reducing IL-4 but increasing IFN-g concentration. IL-4 is responsible for the development of Th2-type immune responses while IFN-g, a Th1 cytokine, inhibits Th2 immune responses. Therefore, modulating Th1 and IL-4 production is helpful to treat asthma. In addition, it attenuates PI3-kinase expression which stimulates expression of IL-8 and chemokines ligand 2 (CCL2) in bronchial epithelial cells and adhesion molecule through inhibiting signaling pathways of Akt,

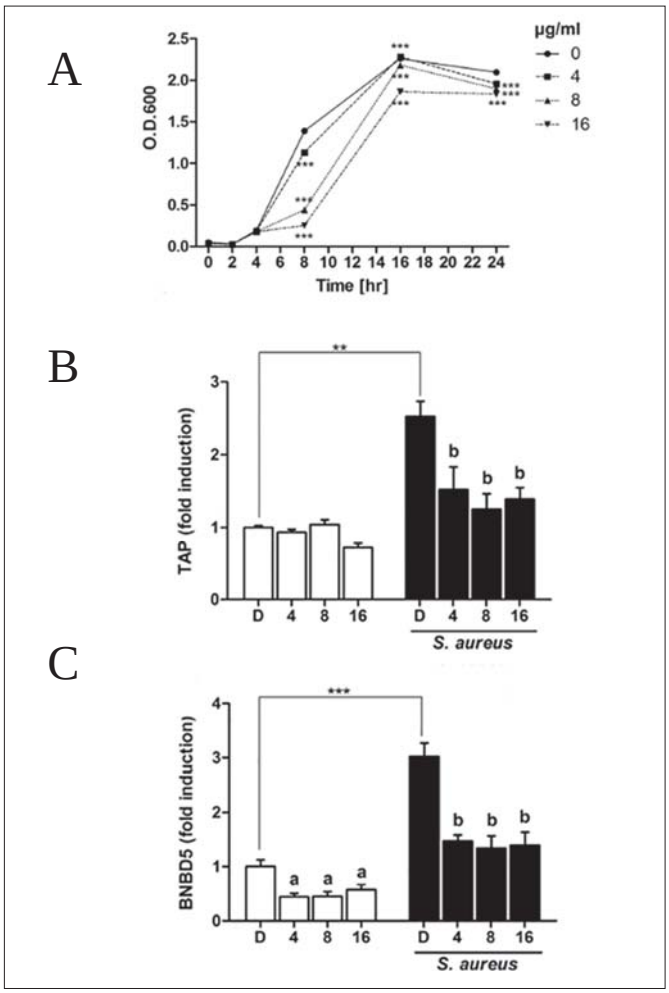

Figure 6. Effect of farrerol on S. aureus growth (A), on the antimicrobial peptide gene expression (B, C). *S. aureus was cultured in MH broth supplemented with different concentrations of farrerol (4-16 mg/ ml)* ***(A)****. Analysis of real-time PCR shows the effect on TAP* ***(B)*** *and BNBD5* ***(C)*** *mRNA expression by bMEC. bMEC were incubated with different concentrations of farrerol (4-16 mg/ml) for 24 h, and then were challenged with S. aureus for 2 h or left untreated* ***(B-C)***[10]

NF-kB ERK-1/2 and JNK. Overexpression of IL-8, CCL2, and adhesion molecules will trigger asthma. It is also important to modulate production of IL-8, CCL2, and adhesion molecules.[12]

4. Kaempferol

Kaempferol is another constituent in Rhododendri Daurici Folium. It is well-known for anti-inflammatory property. It exhibits anti-inflammatory response through blocking the expression of IL-1 beta cytokine which activates the enzymes and genes crucial to the inflammatory response, TNF-induced IL-8 promoter activation, IL-8 gene expression and JAK3 activation which activates signal transducer and activator of transcription 6 (STAT 6) and STAT 5 for production of inflammatory proteins.[13] Owing to the effect in suppressing expression of asthma-induced moecules, it can be a potential medicine for treating asthma.

MODE OF MEDICINAL ACTIVITIES OF RHODODENDRON DAURICUM FOLIUM

Pharmacological investigations indicate that the leaf of *Rododendron dauricum* L. has anti-tussive and expectorant effects. It can inhibit allergic respiratory inflammation. In

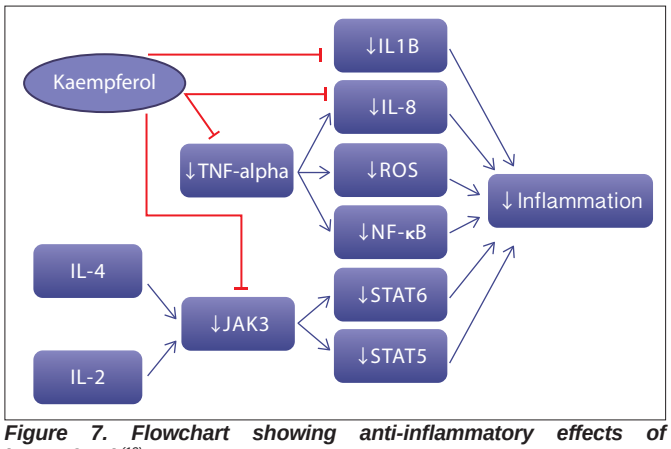

Figure 7. Flowchart showing anti-inflammatory effects of kaempferol.[13]

traditional Chinese medicine, this herb can stop coughing and eliminate phlegm.

SAFETY EVALUATIONS/ CONTRAINDICATIONS

As a herbal medicine with long application history, there are few accidents reported relevant to the undesirable effects of of Rhododendri Daurici Folium. Nevertheless, patients with a history of liver and heart ailments are advised to avoid long-term use since grayanotoxin I, which is the toxin within Rhododendri Daurici Folium, can decrease heart rate[14] and damage the liver tissues.[15] Also it has been suggested that intaking large quantity of volatile oils of Rhododendri Daurici Folium may cause symptoms of nausea, vomiting, dizziness, angina, sweating and asthenia.[16]

DOSAGE

Unless advised by the traditional Chinese medicine practitioners, recommended dosages are 3 - 10 g per dose for decocted one and 15 - 30 g for fresh one.[16]

CONCLUSION

Rhododendri Daurici Folium is widely used as herbal medicine especially in China. This herb originates from the dried leaf of *Rhododendron dauricum* L. It has attracted considerable attentions of many scientific fields due to its low toxicity and therapeutic effect. Owing to the insignificant morphological difference between it and confused species of *Rhododendron*, HPLC analysis should be performed as well as morphological identification. It contains several bioactive constituents, i.e. hyperoside, farrerol, quercetin and kaempferol, which exhibit the bioactivities contributing to its therapeutic effects. As a valuable herbal medicine with long history, further investigation should be conducted on other species of *Rhododendron* in future.

ACKNOWLEDGEMENTS

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Author's background

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Professional Services Advancement Support Scheme (PASS)

Reported by **Matthew H M Wong, Council member, The Pharmaceutical Society of Hong Kong**

On the 30th of August this year, the Commerce and Economic Development Bureau (CEDB) convened a Forum on Professional Services at the Central Government Offices. The Pharmaceutical Society of Hong Kong was invited to attend the forum.

Mr C Y Leung, the Chief Executive, welcomed the attendance of more than 200 representatives from professional bodies, trade and industry organisations and research institutions, as well as members of the Working Group on Professional Services set up under the Economic Development Commission, to the forum. Other government officials attending the forum included Mr Gregory So, the Secretary for Commerce and Economic Development, Mr Paul Chan, the Secretary for Development, and Miss Yvonne Choi, the Commissioner for Belt and Road.

The forum discussed the positive market outlook in Hong Kong, China and beyond for the professional services sector, and how the sector may step up outreaching efforts in line with the 'Belt and Road' Initiative. During the sharing sessions, Mr Raymond Yip, the Deputy Executive Director of the Hong Kong Trade Development Council, talked about business opportunities for Hong Kong professionals in Mainland and other markets on the 'belts'. Representatives from the Hong Kong International Arbitration Centre and the Hong Kong Institute of Architects also shared their experiences in promoting professional services outside Hong Kong with government support.

We learnt that, building on the success of Professional Services Development Assistance Scheme (PSDAS), the CEDB plans to launch a new $200 million Professional Services Advancement Support Scheme (PASS) in the fourth quarter of 2016, and its preparation will take into account views collected from the forum and other channels. The Scheme follows an initiative announced in the 2016 Policy Address and the Legislative Council's funding approval in July. The new Scheme will support Hong Kong professional services in enhancing exchanges and co-operation with their counterparts in external markets, promoting relevant publicity activities, and implementing other projects for enhancing the sector's professional standards and external competitiveness. That should create more job opportunities for HK professional graduates. Views and suggestions on its operation are welcome and may be sent to the CEDB. A vetting committee to be announced will accept and assess applications four time a year.

Forum on Professional Services at the Central Government Offices

PASS Slides

PASS Slides continued

ATOZET
(MSD)

Prepared by Tiffany Yeung, edited by Lucilla Leung

Active Ingredient:
Ezetimibe (10 mg) and atorvastatin (10 or 20 mg)

Presentation:
10 mg/10 mg tablet: Capsule-shaped, biconvex, white to off-white, film-coated, size 12.74 mm x 5.10 mm, "257" debossed on one side
10 mg/20 mg tablet: Capsule-shaped, biconvex, white to off-white, film-coated, size 14.48 mm x 5.79 mm, "333" debossed on one side

Pharmacological Properties:
Lipid modifying agents, HMG-CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA05

Mechanism of action
ATOZET contains ezetimibe and atorvastatin.
The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols. Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Pharmacodynamic effects
Primary Hypercholesterolaemia
In a placebo-controlled study, 628 patients with hyperlipidaemia were randomised to receive placebo, ezetimibe (10 mg), atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/10, 10/20, 10/40, and 10/80)for up to 12 weeks . Patients receiving all doses of ATOZET were compared to those receiving all doses of atorvastatin. ATOZET lowered total C, LDL C, Apo B, TG, and non HDL C, and increased HDL-C significantly more than atorvastatin alone.
Homozygous Familial Hypercholesterolaemia (HoFH)
A double-blind, randomised, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analyzed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline. Increasing the dose of atorvastatin from 40 to 80 mg (n=12) produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/40 and 10/80 pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg. In those patients coadministered ezetimibe and atorvastatin equivalent to ATOZET (10/80, n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg was produced.

Indications:
ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate
- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

Posology and method of administration:
Posology:
Hypercholesterolaemia
The patient should be on an appropriate lipid lowering diet and should continue on this diet during treatment with ATOZET.
The dose range of ATOZET is 10/10 mg/day through 10/80 mg/day. The typical dose is 10/10 mg once a day.
Homozygous Familial Hypercholesterolaemia
The dose of ATOZET in patients with homozygous FH is 10/10 to 10/80 mg daily.
Coadministration with bile acid sequestrants
Dosing of ATOZET should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

Special populations
- *Elderly population:* No dose adjustment is required for older patients.
- *Renal impairment:* No dose adjustment is required for renally impaired patients.
- *Hepatic impairment:* ATOZET should be used with caution in patients with hepatic impairment. ATOZET is contraindicated in patients with active liver disease.
- *Paediatric population:* The safety and efficacy of ATOZET in children has not been established. No data are available.

Method of administration
ATOZET is for oral administration. ATOZET can be administered as a single dose at any time of the day, with or without food.

Contraindications:
- Hypersensitivity to the active substances or to any of the excipients (including lactose).
- Pregnancy and breast-feeding, and women of child-bearing potential not using appropriate contraceptive measures.
- Patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN).

Special warnings and precautions for use:
- Monitoring

Before treatment: CPK level, Liver function tests
During treatment: CPK level, Liver function tests
- Myopathy/Rhabdomyolosis

Cases of myopathy and rhabdomyolysis have been reported in patient taking ezetimibe. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. Also, ATOZET contains atorvastatin, which may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis.

• Hepatic effects

Consecutive transaminase elevations (≥3 times the upper limit of normal [ULN]) have been observed.

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended.

• Hemorrhagic stroke

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo.

• Respiratory reactions

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy.

• Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment.

• Lactose

ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Drug Interactions:

Pharmacokinetic interactions of other medicinal products on ATOZET

Ezetimibe

- *Antacids:* Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.
- *Cholestyramine:* Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. This may lessen reduction of low-density lipoprotein cholesterol (LDL-C).
- *Ciclosporin:* Increase in the mean AUC and exposure of ezetimibe and increase in ciclosporin AUC have been observed in studies. Ciclosporin concentrations should be monitored in patients receiving ATOZET and ciclosporin.
- *Fibrates:* Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold respectively. Although these increases are not considered clinically significant, coadministration of ATOZET with fibrates is not recommended.

Atorvastatin

- *CYP3A4 inhibitors:* Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4). Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin. Coadministration of potent CYP3A4 inhibitors should be avoided if possible. When concomitantly used with moderate CYP3A4 inhibitors, a lower maximum dose of ATOZET should be considered and appropriate clinical monitoring of the patient is recommended.
- *Inducers of cytochrome P450 3A4:* Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 can lead to variable reductions in plasma concentrations of atorvastatin.
- *Transport protein inhibitors:* Atorvastatin is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin
- *Gemfibrozil / fibric acid derivatives:* The use of fibrates alone is occasionally associated with muscle-related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin.
- *Ezetimibe:* The use of ezetimibe alone is associated with muscle-related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.
- *Colestipol:* Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were coadministered than when either medicinal product was given alone.
- *Fusidic acid:* Muscle-related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of ATOZET treatment may be appropriate.
- *Colchicine:* Cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.
- *Boceprevir:* Exposure to atorvastatin was increased when administered with boceprevir. When coadministration with ATOZET is required, starting with the lowest possible dose of ATOZET should be considered with titration up to desired clinical effect while monitoring for safety, without exceeding a daily dose of 10/20 mg. For patients currently taking ATOZET, the dose of ATOZET should not exceed a daily dose of 10/20 mg during coadministration with boceprevir.

Pharmacokinetic interactions of ATOZET on other medicinal products

Ezetimibe

- *Anticoagulants:* There have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione.

Atorvastatin

- *Digoxin:* When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.
- *Oral contraceptives:* Coadministration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethisterone and ethinyl estradiol.
- *Warfarin:* Coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing, which returned to normal within 15 days of atorvastatin treatment.

Side Effects:

Adverse reactions reported with ATOZET (or coadministration of ezetimibe and atorvastatin equivalent to ATOZET) in placebo-controlled studies are shown below. Frequencies are defined as: very common (³1/10); common ³1/100, <1/10); uncommon (³1/1000, <1/100); rare (³1/10,000, <1/1000); and very rare (<1/10,000).

ATOZET		
System organ class	**Adverse reaction**	**Frequency**
Infections and Infestations	influenza	Uncommon
Psychiatric disorders	depression; insomnia; sleep disorder	Uncommon
Nervous system disorders	dizziness; dysgeusia; headache; paraesthesia	Uncommon
Cardiac disorders	sinus bradycardia	Uncommon
Vascular disorders:	hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	dyspnea	Uncommon
Gastrointestinal disorders	diarrhoea	Common
	abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort	Uncommon
Skin and subcutaneous tissue disorders	acne; urticaria	Uncommon
Musculoskeletal and connective tissue disorders	myalgia	Common
	arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity	Uncommon
General disorders and administration site conditions:	asthenia; fatigue; malaise; edema	Uncommon
Investigations:	ALT and/or AST increased; alkaline phosphatase increased; blood creatine phosphokinase (CPK) increased; gamma-glutamyltransferase increased; hepatic enzyme increased; liver function test abnormal; weight increased	Uncommon

Forensic Classification: P1S1S3

Note: This summary does not include all parts of the prescribing information due to limited space. Please refer to the full prescribing information for further details.

every BODY LABO

advanced formula
without a prescription

SOOTHE COLLECTION

body wash / moisturizer / shampoo / conditioner

- SLES/SLS free
- paraben free
- formaldehyde donor free
- dimethicone free
- phthalates free
- sulfate free
- soap free
- ethyl alcohol free
- lanolin free
- dye free
- colors free
- fragrance free

clinically mild for sensitive skin & scalp
fast acting, long lasting itch relief
reduces physical symptoms of redness and dryness
promotes healthy skin and improves the quality of life

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