HONG KONG PHARMACEUTICAL JOURNAL

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News & Short Communications

The Role of Pharmacists in Medical Care of Attention Deficit Hyperactivity Disorder

COVID-19: Update on Evidence for a Pre-Exposure Prophylaxis Strategy versus Post-Exposure Prophylaxis (2 CE Units)

Awareness and Knowledge on Atrial Fibrillation and Oral Anticoagulants of Patients in Hong Kong

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Indication: Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and use of a colloid is appropriate.

References: 1. Curling J, Goss N, Bertolini J. The History and Development of the Plasma Protein Fractionation Industry. In: Bertolini J, Goss N, Curling J, editors. Production of Plasma Proteins for Therapeutic Use. 1st ed. Hoboken, NJ (United States): John Wiley & Sons, Inc.; c2013. p. 3-28. **2.** Kim J. Introducing Takeda's Plasma-Derived Therapies Business [Internet]. Covington, GA (United States): Takeda Pharmaceutical Company Limited; 2019 Nov 15. Available at: https://www.takeda.com/4ab4df/siteassets/system/investors/report/quarterlyannouncements/fy2019/pdt_20191115.pdf. Accessed 2021 Jun 15. **3.** Quality Standards of Excellence, Assurance and Leadership (QSEAL) [Internet]. Annapolis, MD (United States): Plasma Protein Therapeutics Association; c2020. Available at: https://www.pptaglobal.org/safety-quality/standards/qseal. Accessed 2021 Jun 15. **4.** International Quality Plasma Program (IQPP) [Internet]. Annapolis, MD (United States): Plasma Protein Therapeutics Association; c2020. Available at: https://www.pptaglobal.org/safety-quality/standards/iqpp. Accessed 2021 Jun 15. **5.** Data on file. C-APROM/INT//2144, Plasma-Derived Therapeutics Pathogen Safety Monograph, 2018 Sep. Takeda Pharmaceutical Company Limited.

Abbreviated product information (EU Aug17-HK Aug17)
Human Albumin 200 g/l [Baxter/Baxalta] Solution for Infusion
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- OTC & Health
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Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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

Editorial

News & Short Communications

Pharmacy Education & Practice

Drugs & Therapeutics

Society Activities

New Product

Strengthening of Primary Healthcare Services in Hong Kong

On 19 December 2022, the Government released the Primary Healthcare Blueprint to formulate the direction of development and strategies for strengthening Hong Kong's primary healthcare system. With the ageing population and the increasing prevalence of chronic diseases, it is unsustainable to cope with the ever-rising healthcare demand solely through increasing public healthcare expenditure for subsidising public hospital services. Hong Kong needs to introduce a systemic reform of the healthcare system to shift the focus of the present healthcare system from curative treatment to disease prevention.

The Blueprint puts forward five major directions of primary healthcare reform. Key recommendations[1] are:

(1) Develop a community-based primary healthcare system to further develop the district-based, family-centric community healthcare system based on the service model of District Health Centres; to strengthen the concept of "Family Doctor for All"; to introduce the Chronic Disease Co-Care Scheme to provide targeted subsidies to citizens for diagnosis and management of target chronic diseases (in particular hypertension and diabetes) in the private healthcare service sector; and

(2) Strengthen primary healthcare governance: to require all family doctors and healthcare professionals providing primary healthcare services to be enlisted on the Primary Care Register to ensure the quality of primary healthcare services; and to establish a two-way referral mechanism between primary healthcare services and specialist and hospital services, emphasising the case management and gate-keeping role of primary healthcare service providers.

(3) Consolidate primary healthcare resources: to make wider use of market capacity and adopt the "co-payment" principle in providing government-subsidised primary healthcare programmes; to enhance the Elderly Health Care Voucher Scheme and other subsidised services; to oversee the development and implementation of primary healthcare strategic purchasing programmes via the Strategic Purchasing Office; and

(4) Reinforce primary healthcare manpower: to review the manpower projection model and formulate strategies to project the demand for primary healthcare professionals and increase manpower supply; and to strengthen primary healthcare-related training for all primary healthcare service providers and the role of Chinese medicine practitioners, community pharmacists and other primary healthcare professionals in the delivery of primary healthcare services.

(5) Improve data connectivity and health surveillance: to transform the Electronic Health Record Sharing System (eHealth) into a comprehensive and integrated healthcare information infrastructure for healthcare data sharing, service delivery and process management; to require all primary healthcare service providers to use eHealth; and to develop a population-based health dataset and conduct on-going data analytics and surveys to support the Government in formulating healthcare policy.

As pharmacists, we welcome the implementation of this new healthcare reform. To take part as a primary care pharmacist, one must equip oneself with the required training and enroll on the Primary Care Register in due course. Professional Societies and Association may need to negotiate with the Government on the fees for case management, medication review and medication reconciliation services.

LEE, Timothy Pak-Hei; WONG Vincent Kai-Chung; MAK Raymond Wai-Ming; CHUI William Chun-Ming wrote a timely article titled "COVID-19: Update on Evidence for a Pre-Exposure Prophylaxis Strategy versus Post-Exposure Prophylaxis" on page 79. While vaccines against COVID-19 are readily available in Hong Kong, not all individuals mount an adequate immune response to the COVID-19 vaccination series, these individuals may benefit from the use of pre-exposure prophylaxis agents to confer passive immunity against severe acute respiratory syndrome coronavirus 2. Currently, tixagevimab-cilgavimab is the only safe and effective option for pre-exposure prophylaxis for patients expected to have an insufficient immune response to vaccination against COVID-19.

MOK, Hoi Ying; LEE, Lok Tin; YAN, Bryan P; LEE, Vivian WY wrote an article on "Awareness and Knowledge on Atrial Fibrillation and Oral Anticoagulants of Patients in Hong Kong" on page 86. This study evaluated the knowledge about AF and oral anticoagulants (OAC) of the patients attending SOPC at PWH. Patients had inadequate knowledge about AF and OAC, and drug cost was a major factor affecting the choice of OAC in the study population. Furthermore, patients had a passive role in the decision-making process of their disease management.

ESMAEILZADEH MELL, Nadiaa; LAI, Yat Wing Betty; LI, Siu Lam; LEUNG, Yin Mei; SUN, Wai Yan Kiwi wrote an article on "The Role of Pharmacists in Medical Care of Attention Deficit Hyperactivity Disorder" on page 72. Proper management of attention deficit hyperactivity disorder (ADHD) in children and adults can help reduce the symptoms and its associated psychiatric comorbidities. Taking a precedent of other countries, pharmacists have a significant role in managing and supporting ADHD patients to improve their drug treatment outcomes. In Hong Kong, the service gap of clinical pharmacy in medical care for ADHD patients exists, as the trend of prescribing ADHD medications continues to rise. Pharmacist-led ADHD clinic, pharmacist-patient partnership and pharmacist-physician collaboration can be key to improve health services for ADHD patients.

It is encouraging to read about the community services of PSHK, activities and press conference of SHPHK to educate the public. Hope you can take time to read about the articles during the Chinese New Year Holiday. May I take this opportunity to wish you all a Happy, Healthy and Prosperous New Year!

Mary Catherine Cheng
Managing Editor
7 January 2023

Reference

1. www.primaryhealthcare.gov.hk

Vitamin K Antagonist Demonstrated Reduced Composite Cardiovascular Outcome Compared to Rivaroxaban in Patients with Rheumatic Heart Disease-Associated Atrial Fibrillation Without Increasing Bleeding

Date: Sep 15, 2022

The efficacy of factor Xa inhibitors such as rivaroxaban in reducing stroke risk in patients with atrial fibrillation was demonstrated by studies worldwide. However, existing trials have not included patients with rheumatic heart disease-associated atrial fibrillation, which is recommended to be treated by vitamin K antagonist (VKA) according to current guidelines.

INVICTUS is an international, randomized trial in Africa, Asia, and Latin America that compared the cardiovascular outcomes of rivaroxaban and VKA therapy among patients with atrial fibrillation and echocardiographically documented rheumatic heart disease. Enrolled patients had at least one of the following: a CHA_2DS_2VASc score ≥2, a mitral-valve area ≤2 cm^2, left atrial spontaneous echo contrast, or left atrial thrombus. A total of 4565 patients were randomly assigned to receive standard doses of rivaroxaban (n=2292) or dose-adjusted VKA (n=2273). Primary efficacy outcomes included a composite of stroke, systemic embolism, myocardial infarction, and death from vascular or unknown causes. Primary safety outcome was major bleeding according to the International Society of Thrombosis and Hemostasis.

In the intention-to-treat analysis, 8.21% (560 of 2275) and 6.49% (446 of 2256) of patients encountered a primary efficacy outcome event in the rivaroxaban group and VAK group, respectively (proportional-hazards ratio, 1.25; 95% confidence interval [CI], 1.10 to 1.41; P<0.001). Additionally, the Kaplan-Meier survival curve was non-proportional, thus a restricted mean survival time analysis was conducted. The restricted mean survival time was 1599 days in the rivaroxaban group and 1675 days in the VKA group (difference, −76 days; 95% confidence interval [CI], −121 to −31; P<0.001). Rates of major bleeding were similar between the treatment groups (proportional-hazards ratio, 0.76; 95% CI, 0.51-1.15; P=0.18).

This study showed that vitamin K antagonist therapy compared to rivaroxaban, led to a significantly lower rate of a composite of cardiovascular events or death without increasing the incidence of major bleeding among patients with rheumatic heart disease-associated atrial fibrillation. Thus, this trial supports current guideline recommendations on vitamin K antagonist therapy for the prevention of stroke in patients with rheumatic heart disease-associated atrial fibrillation.

Source: www.nejm.org

Bionic Pancreas Demonstrated Lower Glycated Hemoglobin Levels than Standard Insulin Therapy in Patients with Type 1 Diabetes

Date: Sep 29, 2022

Commercially available hybrid closed-looped insulin delivery systems require individualized insulin regimens for the initialization of therapy and meal carbohydrate counts to determine mealtime insulin doses. In contrast, the bionic pancreas automates the determination and delivery of all insulin doses based on body weight and qualitative carbohydrate estimates at mealtime.

This 13-week, multicenter, parallel-group, unblinded, randomized trial across 16 centers in the United States examined the efficacy and safety of a bionic pancreas as compared with standard care in children and adults with type 1 diabetes. A total of 326 type 1 diabetic patients, aged 6 or above, were randomly assigned in a 2:1 ratio to receive automated glucose control with a bionic pancreas (with insulin aspart or insulin lispro) or to receive standard care (defined as any insulin-delivery method with unblinded, real-time continuous glucose monitoring). The primary outcome was the glycated hemoglobin (HbA1C) level at 13 weeks. The secondary outcome was the percentage of time glucose level was below 54 mg per deciliter measured by the continuous glucose monitor. Safety outcome was assessed as well.

The mean HbA1C level decreased from 7.9% to 7.3% in the bionic pancreas group while the level remained the same (remained 7.7% at baseline and at week 13) in the standard care group (mean adjusted difference at 13 weeks, -0.5 percentage points; 95% confidence interval [CI], -0.6 to -0.3; P<0.001). Secondary outcomes did not differ significantly between the two groups (13-week adjusted difference, 0.0 percentage points; 95% CI, −0.1 to 0.04; P<0.001 for noninferiority). The rates of severe hypoglycemia were also similar with 17.7 and 10.8 events per 100 participant-years in the bionic pancreas and standard care group, respectively (P=0.39). No incidence of diabetic ketoacidosis occurred in either group.

In conclusion, therapy using automated glycemic control with a bionic pancreas resulted in lower HbA1C levels than standard insulin therapy augmented by continuous glucose monitoring in adults and children with type 1 diabetes.

Source: www.nejm.org

Acetazolamide Demonstrated Benefits in Acute Decompensated Heart Failure with Volume Overload

Date: Sep 29, 2022

Residual symptoms of fluid overload were often found despite the use of high-dose intravenous loop diuretics in patients with acute decompensated heart failure. There was yet a lack of evidence to support other add-on diuretics for their efficacy to benefit patients with a more efficient decongestion.

In this multi-center parallel-group double-blind randomized placebo-controlled ADVOR trial, acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, was assessed for its efficacy in successful decongestion, which was defined as an absence of clinical signs of volume overload within 3 days. Death from any causes or rehospitalization for heart failure during 3 months of follow-up were also assessed as secondary endpoints.

A total of 519 patients with acute decompensated heart failure, clinical signs of volume overload, and elevated N-terminal pro–B-type natriuretic peptide level or B-type natriuretic peptide level, were randomized to receive either intravenous acetazolamide 500 mg once daily or placebo as an add-on to the standard regimen of intravenous loop diuretics. All participants were neither receiving acetazolamide maintenance therapy, treatment of sodium–glucose cotransporter 2 (SGLT2) inhibitor, nor having a systolic blood pressure of less than 90 mmHg or an estimated glomerular filtration rate (eGFR) of less than 20 mL/min/1.73 m^2. Successful decongestion was demonstrated in 108 out of 256 patients (42.2%) in the acetazolamide group and in 79 out of 259 (30.5%) in the placebo group (risk ratio, 1.46; 95% confidence interval [CI], 1.17 to 1.82; P<0.001). Death from any cause or rehospitalization for heart failure occurred in 29.7% and 27.8% of the patients in the acetazolamide group and placebo group respectively (hazard ratio, 1.07; 95% CI, 0.78 to 1.48). The acetazolamide group reported a higher cumulative urine output and natriuresis indicating better diuretic effect. The number of reported cases of adverse events including deterioration of kidney function, hypokalemia, and hypotension was found to be similar between the two groups.

The study concluded that the addition of acetazolamide to loop diuretic therapy in patients with acute decompensated heart failure could result in a higher rate of successful decongestion. To further establish the relationships between acetazolamide and the degree of decongestion and quality of life in patients with acute decompensated heart failure, more trials with larger sample sizes were warranted.

Source: www.nejm.org

FDA Approved First Fecal Microbiota Product Rebyota for Prevention of *Clostridioides difficile* infection

Date: Nov 30, 2022

The U.S. Food and Drug Administration (FDA) announced their approval of the first fecal microbiota product, Rebyota, for the prevention of recurrence of *Clostridiodes difficile (C. difficile)* infection in patients aged at least 18 years old.

C. difficile infection (CDI) may cause diarrhea, colitis and fever, and in severe cases, organ failure and death. Risk factors for CDI include antibiotics use, aged 65 years or above, hospitalization, immunocompromised and a prior history of CDI. Since the intestinal tract contains millions of microorganisms, which is known as the “gut flora” or “gut microbiome”, antibiotics use may change the balance of the “gut flora” resulting in recurrent CDI. It was believed that an infected patient may be prone to recurrent CDI unless the “gut flora” has been restored.

To facilitate normalisation of the gut environment, Rebyota, which was prepared from stool donated by qualified individuals, was investigated and manufactured. Transmissible pathogens were screened during the manufacturing process to reduce possible infection risk. Yet, Rebyota may still contain other infectious agents or unknown food allergens which could be a concern. The safety of Rebyota was assessed in two randomized, double-blind, placebo-controlled clinical studies and in open-label clinical studies conducted in the U.S. and Canada. Participants who had a history of recurrent CDI received one or more doses of Rebyota rectally or placebo at 24 to 72 hours after completion of antibiotic treatment for their CDI. The most common side effects reported by one study with 180 Rebyota recipients were abdominal pain, diarrhea, abdominal bloating, gas and nausea.

The effectiveness of Rebyota was evaluated in a randomized, double-blind, placebo-controlled, multicenter study. The overall estimated success rate in preventing recurrent CDI through 8 weeks was higher in the Rebyota group (70.6%) than in the placebo group (57.5%). The significant results brought Rebyota to be an additional approved option for patients suffering from recurrent CDI.

Source: www.fda.gov

Empagliflozin Reduced Risk of Progression of Chronic Kidney Disease

Date: Dec 11, 2022

Emerging studies showed that empagliflozin could benefit patients with diabetic kidney disease and albuminuria to reduce the risk of progression to kidney failure. However, the majority of chronic kidney disease (CKD) patients does not show a high level of urinary albumin-to-creatinine ratio and are not diabetic.

The EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) study, an international, randomized, parallel-group, double-blind, placebo-controlled, clinical trial, was hence conducted to evaluate the effects of the sodium–glucose co-transporter 2 (SGLT2) inhibitors empagliflozin in patients with CKD. Patients with CKD who had an estimated glomerular filtration rate (eGFR) of 20 to 45 mL/min/1.73 m^2, or who had an eGFR of 45 to 90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio of at least 200, but without polycystic kidney disease or kidney transplanted, were recruited and randomized to receive empagliflozin 10 mg once daily or placebo. The primary outcome was defined as the occurrence of a sustained decrease in the eGFR to less than 10 mL/min/1.73 m^2 or for at least 40% from baseline, or death from renal causes. The rate of hospitalization for heart failure or death from cardiovascular causes was also analysed as secondary outcomes.

Among 6609 participants, the progression of kidney disease or death from cardiovascular causes occured in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001) during a median of 2.0 years of follow-up. Consistent results were found without regard to the presence of diabetes or eGFR ranges. No significant differences in the rate of hospitalization for heart failure or death from cardiovascular causes (4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1% respectively).

The results from the EMPA-KIDNEY trial implied that empagliflozin therapy could lead to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo among a wide range of patients with chronic kidney disease. Clinical labelled use of empagliflozin as an adjunctive agent in CKD patients was prospected.

Source: www.nejm.org

Government releases Primary Healthcare Blueprint

Date: Dec 19, 2022

The Government released the Primary Healthcare Blueprint on 19 December 2022 to formulate the direction of development and strategies for strengthening Hong Kong's primary healthcare system. With the ageing population and the increasing prevalence of chronic diseases, the healthcare cost is forever increasing in the public hospital services. Hong Kong needs to introduce a systemic reform of the healthcare system to shift the focus of the present healthcare system from curative treatment to disease prevention.

The Blueprint puts forward five major directions of primary healthcare reform. Key recommendations are listed below:

(1) Develop a community-based primary healthcare system: to further develop the district-based, family-centric community healthcare system based on the service model of District Health Centres; to strengthen the concept of "Family Doctor for All"; to introduce the Chronic Disease Co-Care Scheme to provide targeted subsidies to citizens for diagnosis and management of target chronic diseases (in particular hypertension and diabetes) in the private healthcare service sector; and

(2) Strengthen primary healthcare governance: to require all family doctors and healthcare professionals providing primary healthcare services to be enlisted on the Primary Care Register to ensure the quality of primary healthcare services; and to establish a two-way referral mechanism between primary healthcare services and specialist and hospital services, emphasising the case management and gate-keeping role of primary healthcare service providers.

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Source: www.primaryhealthcare.gov.hk

The Role of Pharmacists in Medical Care of Attention Deficit Hyperactivity Disorder

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ABSTRACT

Proper management of attention deficit hyperactivity disorder (ADHD) in children and adults can help reduce the symptoms and its associated psychiatric comorbidities. Taking a precedent of other countries, pharmacists have a significant role in managing and supporting ADHD patients to improve their drug treatment outcomes. The general healthcare system cost can also be reduced after implementing the pharmacy services. In Hong Kong, the service gap of clinical pharmacy in medical care for ADHD patients exists, as the trend of prescribing ADHD medications continues to rise. Pharmacist-led ADHD clinic, pharmacist-patient partnership and pharmacist-physician collaboration can be key to improve health services for ADHD patients.

Keywords: *ADHD, medication management, pharmacist intervention, multidisciplinary collaboration*

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a psychiatric and neuro-developmental disorder that is prevalent in the paediatric population. In Hong Kong, 6.4% of children and adolescents, and 2.5% of adults are diagnosed with ADHD.[1] Characterized by a persistent pattern of inattention, hyperactivity and impulsivity, ADHD is often manifested as excessive fidgetiness, restlessness, excessive talking, difficulty in organisational tasks, and forgetfulness.[2] However, a heterogeneous clinical presentation is usually observed in adults, transcending typical motor symptoms to a wider spectrum of emotional dysregulation and functional impairment.[3]

ADHD has a significant long-term impact on individuals and society. Mismanagement of ADHD in children can aggravate the negative impacts of ADHD and its psychiatric comorbidities, such as depressive and anxiety disorders.[4] Inattentiveness may limit the opportunities for children with ADHD to acquire social skills or to attend to social cues necessary for effective social interaction. Hyperactive and impulsive behaviours may result in peer rejection.[5] According to the National Comorbidity Survey, adults with ADHD are three times more likely to develop major depressive disorder, six times more likely to develop dysthymia, greater than four times more likely to have any mood disorder,[6] and twice as likely to experience substance abuse or dependence.[7] In short, ADHD is often perceived as causal to behavioural problems in various settings, and if left untreated, the effects tend to persist in adulthood and lead to poor health, academic, and psychosocial outcomes.

Since no local guidelines on the management of ADHD in Hong Kong are available, local practice is informed by international guidelines.[8] The use of psychostimulants is the first-line treatment option for ADHD patients.[9] Methylphenidate is the most commonly prescribed medication for the management of ADHD in Hong Kong, Taiwan, Canada, Finland and Spain.[1] Other pharmacological options include atomoxetine and amphetamine.[10] Behavioural treatment, psychoeducation and parent management training are examples of non-pharmacological intervention, however their efficacy as mono- or combined therapy is not full examined.[9,11,12,13]

In recent years, the use of medications for ADHD has increased worldwide.[1] In Hong Kong between 2001 and 2015, the use of ADHD medications has increased 36 times in children and tripled in adults.[1,14] The increase of medication prescription rate can be explained by enhanced awareness of ADHD among parents and educators.[14] Medications are most commonly prescribed for children between 6 and 11

years old, probably due to the high expectation of good discipline in Hong Kong primary schools.[14] Indeed, proper use of ADHD medications are very important to ensure the efficacy and safety in the patients. Pharmacists can work collaboratively with physicians to reduce the healthcare-related issues for better ADHD management in children and adults. This article reviews the role of pharmacists in the medical care of ADHD overseas, which may inspire the development of such services in Hong Kong.

Evidence for the Benefit of Pharmacist Services in ADHD management

The role of pharmacists in medical care of ADHD is developed in some countries such as the United States and United Kingdom **(Table 1)**. The benefits of pharmacist services span from improving timely access to initiation and optimization of ADHD therapy, and significant financial savings.

Pharmacist-run ADHD specialty clinic in the United States (US)[15]

In 2017, a pharmacist-run ADHD specialty clinic was established at Campus Health, the college health centre in University of North Carolina at Chapel Hill, which allowed pharmacists to conduct collaborative initial visits with a psychiatrist and independently provide medication management follow-up appointments for students and postdoctoral students with ADHD and other comorbid psychiatric conditions. The initial appointment co-visit model began with the pharmacist independently reviewing the patient's medical history, measuring the patient's blood pressure and heart rate, assessing for comorbid mental health conditions, followed by a treatment plan made in conjunction with the psychiatrist. At the follow-up appointments, the pharmacist monitored blood pressure and heart rate, assessed medication adherence, evaluated for adverse medication effects, assessed for changes in mood and adjusted the treatment plan when needed.

By implementing this novel partnership between pharmacists and psychiatrists in the ADHD clinic, the total number of patient appointments increased by 1003%, from 26 to 287, over a period of 3 years. Quality of care provided to patients was also improved in the pharmacist-run appointments through increased adherence to blood pressure monitoring policies (77% vs. 11%, P< 0.001) and heart rate monitoring (75% vs. 6%, P<0.001) compared with psychiatrist-run appointments. Positive feedback to pharmacists were received from patients regarding appointment availability, the ability for more frequent follow-up as well as thorough patient education. This demonstrated that pharmacists played an important role in assisting psychiatrists in the medication management of ADHD and optimizing patient outcomes, especially in the college health setting.

Developing a pharmacist prescribing role in UK[16, 18]

Due to the high vacancies in medical staff, child and adolescent mental health services in the UK were unable to achieve the waiting time target for ADHD titration. Patients needed to wait up to 7 months to commence medication after diagnosis, which had a significant negative impact on their quality of life. A project was conducted to utilize the skills of pharmacists to initiate medication and review the response of ADHD patients.[16] Independent prescribing pharmacists undertook the following training over a period of 8 weeks: shadowing

Table 1. Summary of integration of pharmacists on managing ADHD in foreign countries

Country and Year	Pharmacists' Involvement	Outcomes at a Glance
UK, 2021[18]	Integration of pharmacist independent prescribers into child and adolescent mental health services: - Prescription transcribing, wellbeing assessment, monitoring of physical health parameters and provision of medicines-related advice by pharmacist independently	• 62% of the multidisciplinary team members indicated the pharmacist service was extremely beneficial • 6% of pharmacist interventions identified that patients needed to stop ADHD medication • 26% of pharmacist interventions identified that dose change of ADHD medication was needed. Of the 26%, 77% was dose increase owing to suboptimal therapy.
US, 2021[15]	Implementation of a community-based pharmacist-run ADHD clinic in a college health centre: - Pharmacists conducted collaborative initial visits with psychiatrists and independently provided follow-up appointments for patients with ADHD	• Increase in total number of patient appointments by 1003% in 2 years • Improve quality of care to patients, such as more than 75% of patients had blood pressure and heart rate measurements during pharmacist-run appointments
UK, 2019[16]	Development of a pharmacist prescribing role within child and adolescent mental health services (CAMHS): - Initiate medication as independent pharmacist prescriber and review response	• Over a 6-month period, pharmacists initiated ADHD medication to 78 patients, and titrated doses for 36% of the patients who attended the pharmacist clinic.
UK, 2007[17]	Employment of mental health pharmacists to work with child and adolescent mental health services: - Optimize key ADHD medicines by pharmacists	• Reduction in medication expenditure by 133,00 British pounds annually in Child and Adolescent Mental Health Services (CAMHS) over multiple centres across Sussex, UK

clinics; review of national and local guidelines and other readings; accessing IT systems; measuring height, weight and blood pressure; attending training sessions; and appointing patients to the pharmacist-led clinic. After the symptoms of ADHD were assessed, pharmacists initiated the most appropriate medication at the lowest dose as per the local protocol. The medication was then reviewed and adjusted at appointments every 2 weeks for 4–5 appointments. Upon completion of the medication titration, a request was sent to the GP to commence repeat prescribing on a regular dose.[16]

The independent prescribing pharmacists were able to review the waiting list and initiated ADHD medication in 78 patients, who had waited for more than 6 months after diagnosis.[16] As the pharmacist service continues, the waiting time for initiation of medication to treat ADHD is likely to reduce. In addition, the prescribing pharmacists also helped with discussing issues with high-risk medications, monitoring physical health parameters, providing medication review consultations, switching to cost-effective medication and resolving medicines-related queries.[18] A survey of a pharmacist-led ADHD clinic was sent to patient family and healthcare professionals (psychiatrists, psychologists, administrative staff, nurses and social workers) for their satisfaction evaluation.[18]

Employment of mental health pharmacists to work with child and adolescent mental health services in UK[17]

A financial evaluation was conducted on the employment of the first mental health pharmacist in child and adolescent mental health services across Sussex in 2007–2008, by comparing the annual expenditure on medication between years 2004–2005 and 2014–2015. Key expenditure reduction initiatives undertaken or led by the pharmacist were also identified.

Results show that the annual drug expenditure had remained steady in the preceding 3 years and employing pharmacists since 2007 had led to a gradual and consistent reduction in over 7 years, eventually reducing drug spend from baseline by over £133,000 annually. The amount was significantly more than the £36,000 per year which was the cost to employ the pharmacist and indicated a net saving of £97,000 per year. The reduction was achieved by optimizing medication use and through initiatives introduced by the pharmacist. Examples include promoting the use of stimulant ADHD medication only on school days if appropriate and helping appetite-suppressed youngsters to gain weight and mitigate the risk of suboptimal growth. Moreover, pharmacists organized and reported the results of audits against shared care guideline standards for ADHD treatment. Patients were given an annual break in treatment to assess continuing benefit so more patients had their medication discontinued when they could no longer require the medication.

Current Healthcare and Education System Issues Related to ADHD Management in Hong Kong

Most patients receive ADHD treatment via the Hospital Authority in Hong Kong, but the waiting time for the first appointment varies from a few months to a year.[20] The long waiting time may affect the patients' mental status. Some patients with late diagnosis wish that they could receive treatment earlier, as it may limit the emotional problems they experienced in childhood.[12] Although medication is the first-line treatment in Hong Kong, patient response to ADHD medications varies. Sub-therapeutic response and side effects are often reported.[21] Patients may hesitate to discuss medication-related problems with the physician as the physician often changes at each consultation.[21] Furthermore, some patients were not even aware of the options of non-pharmacological therapy.[21]

Local ADHD management is informed by various international guidelines, which may not be entirely suited to the local population and healthcare system. A study has shown that there are challenges when implementing a US ADHD guideline into the UK clinical setting.[22] This suggests that physicians in Hong Kong may also experience difficulty when implementing the guidelines from other countries. As guidelines and studies have shown the potential benefits from a combination of behavioural and drug therapies,[9] some local patients may not have the opportunity to receive the behavioural therapy due to the limited resources. Besides, it may not be feasible to record side effects at each dose change or obtain health outcome feedback from teachers of the ADHD patients as per the NICE guidelines.[9,22] These difficulties are likely to be the same in Hong Kong due to the high workload of physicians and school teachers.

Gaps for Pharmacist-Led ADHD Management Services in Hong Kong

With the rising prescriptions for ADHD medications in Hong Kong and the overburdened healthcare system, there is a great opportunity to identify innovative and sustainable methods for pharmacists to contribute to ADHD management. Apart from physicians, nurses and psychologists, pharmacists are key members of the healthcare team and are experts in managing drug therapy. Pharmacists are therefore ideally positioned to contribute to alleviating the burden related to ADHD through the provision of effective pharmaceutical care as well as patient empowerment. The benefits of pharmacist involvement are discussed below.

Patient-Pharmacist Partnership in ADHD Management

In the context of ADHD patients, treatment alliance is essential to long term adherence.[23] For children and adolescents, the relationship between parents

and health professionals as well as their perception of medication therapy is crucial in determining the patients' medication adherence.[24] Parents' lack of understanding of the effectiveness and possible adverse effects of ADHD medication, and their negative perception of pharmacological management are predictors of lower long-term continuation of treatment.[23] In contrast, increased knowledge about ADHD and the belief that ADHD medication is safe and effective are associated with greater willingness to continue the drug therapy.[24] It is therefore fundamental for pharmacists to utilize their expertise to empower ADHD patients and carers by providing knowledge about ADHD pharmacological treatment and medication-related information.

Since medication adherence is a process that can fluctuate over time, it is crucial for pharmacist to identify and address patients' concerns to enhance patient adherence. One noteworthy factor that could result in medication discontinuation is the transition of healthcare decisions from parents to young ADHD patients as they enter adulthood.[25] It is therefore suggested to include children as active participants in discussing treatment options and pharmacological plan to aid long-term medication adherence especially during their transition into adolescents and adulthood.[26] Pharmacists should also develop a comprehensive understanding of young patients' concerns toward their ADHD treatment, identify their priorities and provide options to provide optimized as well as patient-centred care.

ADHD Psychopharmacological Education

The effectiveness of psychopharmacological education to promote medication adherence and treatment engagement in ADHD pharmacological treatment is documented.[27,28] According to its definition, psychoeducation is a therapeutic method which aims to strengthen children's, parents/carers', school personnel's and other related individuals' understanding of the illness through systemic and didactic communication. Furthermore, pharmacists are proven to play a significant role in providing effective ADHD medication education.[29] Collaboration of pharmacists and other healthcare professionals to deliver psychoeducation that target medication receptivity is therefore a supplementation to optimise ADHD management.

In Chinese society, the ADHD label may have a stigmatizing effect.[30] A study in Taiwan found a significant correlation between affiliate stigma and the unfavourable attitude of patients towards ADHD diagnosis and pharmacological treatment, which can hinder patients' disease management. An elevated level of perceived social stigma toward ADHD is also associated with low inclination to receive pharmacological intervention and poor medication adherence.[31] Considering the above, the need of community outreach and public health education should be emphasized to address public and self-stigma related to ADHD.

Regarding pharmacists' role in ADHD education, studies suggest that pharmacists are useful assets in the healthcare system to deliver mental health education to the public.[32,33] With pharmacist providing accurate knowledge about ADHD, such as its medication and treatment options through pharmacist-led campaigns and educational programmes, stigma surrounding ADHD medication can be reduced. As a result, it is important to further explore the best content and most appropriate method of communication with the public.

Pharmacist-Psychiatrist Collaboration

Another potential intervention by pharmacists is via the establishment of a pharmacist-psychiatrist collaborative clinic. The only published example is the implementation of a community-based pharmacist-led ADHD clinic in a college health centre in the United States.[15] Pharmacists are responsible for conducting collaborative initial visits with psychiatrists and are involved in psychiatric evaluation, medication management, counselling, referral and independent follow-up appointments. Although the healthcare landscape in Hong Kong is different from that of the US, there is potential to take reference from such a model to improve quality of care and adherence to treatment. It is also possible to replicate similar programmes or models currently implemented in Hong Kong such as the diabetic clinic model, which had demonstrated Improvement in patient clinical outcomes with the addition of pharmacists' intervention.[34]

One of the prerequisites of an efficient healthcare cooperation is to have clearly defined guidelines to ensure service delivery. Yet, in Hong Kong, guidelines or protocols for managing ADHD patients are incomprehensive and not standardized.[21] It is thus essential to develop a clear and standardized protocol for assessment, referral, and follow-up of ADHD patients when designing the pharmacist-led ADHD medication management model.

Research regarding pharmacist-led medication management for ADHD children is not yet sufficient. There is literature supporting the benefit of such programmes in adult ADHD patients in improving accessibility of ADHD treatment as well as increasing the likelihood of positive clinical outcomes.[19] Such co-management programmes are usually designed for adult patients because transition to adulthood is a high-risk period for poor medication adherence.[35] In addition, adult ADHD patients are found to have a higher risk of medication diversion, rendering a need to provide pharmacist intervention particularly for young adults with ADHD.[36]

Medication review and adherence assessment should be conducted in a phase- or group-specific manner.[34] For instance, the timeline for assessing patients' understanding of their medications, as well as adherence to therapy, could be divided into initiation, implementation, and discontinuation phases, while the assignment of a pharmacist to patients should be based on clinical needs. Upon disease diagnosis, patients could be referred to pharmacist-managed ADHD program for detailed drug counselling and to consolidate the therapy goals with patients. Patient's health status, disease history and the presence of drug or substance abuse should be assessed to determine their suitability of joining the programme. After the first visit, medication reviews and monitoring should be done monthly with pharmacists until stabilization of drug dose. The final phase could constitute therapy monitoring and tailored interventions to facilitate patient's adherence to medication by a minimum of one visit per year by pharmacists. Pharmacists should monitor and counsel on management of side effects which often help maintain patient willingness to continue ADHD medications.[26] Pharmacists should report any new symptoms or changes and refer to a psychiatrist for further disease evaluation if needed.

Barriers Related to Implementation of Pharmacy Services in ADHD Management

Amid the notable needs to expand pharmacists' intervention, it is crucial to identify and address barriers for successful service implementation and development of the role of pharmacist in ADHD management.

Patient Engagement

Patient engagement is a big factor in determining the success of the pharmacist-led ADHD medication interventions and education. Patients who believe in their healthcare provider and the general healthcare system are more inclined to engage in related services.[37] A local study discovered that Hong Kong citizens do not have a clear understanding of the pharmacist's role and are less likely to consult a pharmacist for their disease management.[38] This may negatively affect patient confidence in pharmacist-led clinical services in ADHD management.

Multidisciplinary Collaboration

Despite supporting evidence for the benefit of pharmacist interventions for patient outcomes, pharmacists are often underutilized on the healthcare team. Although multidisciplinary teamwork is found to benefit patient's health status and treatment compliance, it is challenging to implement collaborative roles for pharmacists within the mental healthcare setting.[39] Major obstacles include different professional cultures and values, insufficient understanding of each other's roles within the team, conflicts of interest and territoriality.[40] It is therefore critical to develop a comprehensive co-management process with clearly defined roles, and to address these communication challenges to maximise operational effectiveness.

Community and Health System Level

Crucial factors to consider for the co-management service model include the cost of service, follow-up intervals between appointments, frequency of psychiatrist and pharmacist consultation, as well as measurement of long-term clinical and economical outcomes.[16] Complicated bureaucratic and administrative procedures may be a hindering factor to establish collaborative services.[41] For economic considerations, limits on healthcare budget, allocated funding (government and non-government), availability of financial incentives for service provision and inter-professional collaboration are elements affecting the implementation of such services.[37]

Consideration of the aforementioned factors is essential when designing innovative healthcare, which involves the expansion of pharmacists' role within the interdisciplinary teams to aim to achieve all-rounded ADHD patient care.

CONCLUSION

ADHD is a prevalent condition in Hong Kong with significant impact on individual and society. Pharmacist services are not currently integrated in the local healthcare team in the management of ADHD, despite international literature in support of the pharmacists' benefits on clinical outcomes and medication expenditure. This article outlined the potential roles for pharmacists in the management of ADHD and the factors to consider in successful implementation. There is an opportunity to improve the quality of ADHD management and reduce healthcare system burden through the incorporation of pharmacist services in Hong Kong.

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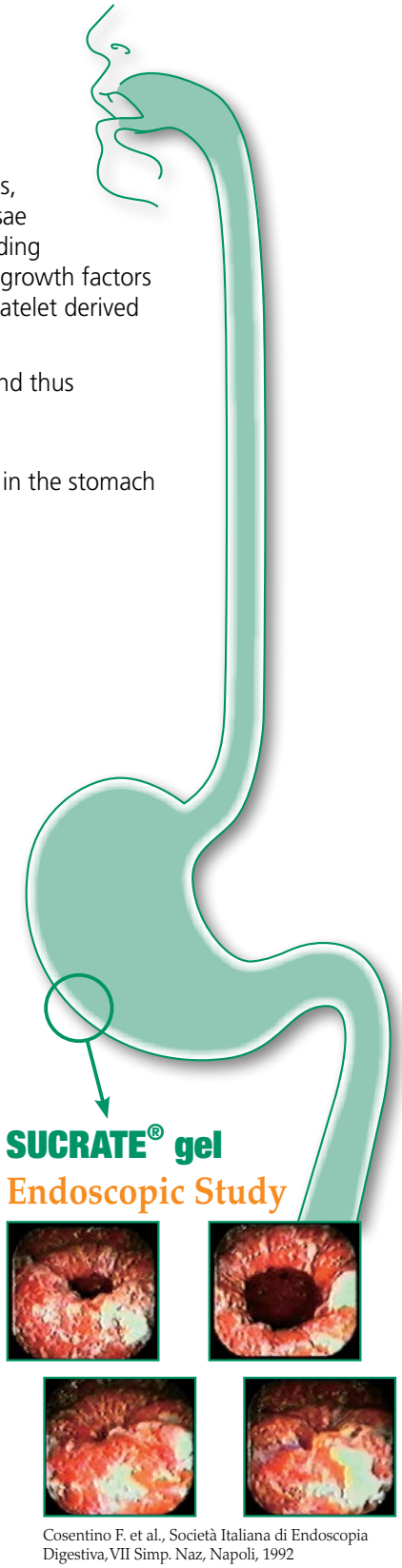

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COVID-19: Update on Evidence for a Pre-Exposure Prophylaxis Strategy versus Post-Exposure Prophylaxis

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has devastated virtually all countries around the world. While vaccines against COVID-19 are readily available in Hong Kong, not all individuals mount an adequate immune response to the COVID-19 vaccination series. These individuals may benefit from the use of pre-exposure prophylaxis agents to confer passive immunity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this article, pre-exposure prophylaxis against COVID-19 will be discussed, with an emphasis on the dual monoclonal antibody combination therapy – tixagevimab and cilgavimab (Evusheld™). Emerging data evaluating the efficacy of this agent in prevention of COVID-19 during the Omicron-dominating phase of the pandemic will also be reviewed.

Keywords: *COVID-19, SARS-CoV-2, Pre-exposure prophylaxis, Omicron variant, Tixagevimab-cilgavimab*

SARS-COV-2 VARIANTS: FOCUSING ON OMICRON

Previously dominating COVID-19 variants have been overtaken by the Omicron variant, which has a replication advantage over previously prevailing Alpha, Beta and Delta variants. At the time of writing (August 2022), the Omicron variant is the only remaining Variant of Concern (VOC) under the U.S. and other VOCs have been demoted to Variant Being Monitored (VBM).[1] The Omicron variant (B.1.1.529) was first detected in the African country Botswana back in November 2021, and has since developed multiple subvariant lineages with various degrees of dominance in circulation around the world.[2] The first-to-emerge BA.1 variant had over 30 mutations in its spike region and over 20 mutations residing in sequences that encode for other viral proteins, when compared to the genome of the Ancestral Wuhan-Hu-1 strain.[3,4] Subvariants BA.4 and BA.5 which is now dominant in many parts of the world contains identical spike proteins, carrying additional 69–70 deletion, L452R, F486V and Q493R mutations.[5] These two sub-lineages have higher transmissibility and could evade neutralising antibodies, contributing to immune escape.[6]

PRESSING NEED FOR PRE-EXPOSURE PROPHYLAXIS AGAINST COVID-19

Certain populations do not mount an adequate immune response against COVID-19 vaccination series. In general, seroconversion rates were significantly lower among immunocompromised individuals e.g. solid organ transplant recipients and patients with haematological disorders.[7] In general, immunocompromised population hospitalised with COVID-19 suffers from greater mortality and worse patient outcomes e.g. need for ICU admissions.[8–10] Unfortunately, the state of immunosuppression is associated with inadequate antibody response to COVID-19 vaccination. Therefore, pre-exposure prophylaxis via passive infusion or injection of antibodies against COVID-19 becomes crucial for vaccine non-responders or poor responders.

Monoclonal antibodies against SARS-CoV-2 mimic the ability of our immune system to combat the virus. They can confer passive but immediate protection against the infection and are therefore heavily studied for both the treatment and prevention of COVID-19.[11] Earlier in the pandemic, the role of bamlanivimab monotherapy in preventing COVID-19 among high-risk individuals in nursing facilities was explored.[12] While a single intravenous infusion of bamlanivimab significantly reduced the incidence of COVID-19 among nursing home workers or residents by almost half (8.5% in treatment arm *versus* 15.2% in placebo arm), bamlanivimab was neither used as prophylaxis nor treatment of COVID-19 as *in vitro* data suggests that it is unable to neutralise the now-prevailing Omicron variant.[13] Another monoclonal antibody cocktail which consists of casirivimab and imdevimab (REGEN-COV™) was originally evaluated

for its efficacy and safety as pre-exposure prophylaxis of COVID-19 in a phase III trial, but the trial was terminated in May 2022 as both components of REGEN-COV™ have failed to inhibit the replication of Omicron variant.[13,14]

EVUSHELD™ (TIXAGEVIMAB-CILGAVIMAB)

On December 8, 2021, the FDA issued an Emergency Use Authorisation for tixagevimab-cilgavimab (Evusheld™) for pre-exposure prophylaxis (PrEP) of COVID-19.[15] Currently, this monoclonal antibody combination is the only agent being granted an EUA for PrEP of COVID-19. The following section will explore the pivotal clinical trials supporting its use as PrEP and furthermore, whether it has additional roles in managing COVID-19.

Mechanism of Action

Evusheld™ consists of a combination of two recombinant human IgG1k monoclonal antibodies, tixagevimab and cilgavimab, both targeting the spike protein of SARS-CoV-2. Both monoclonal antibodies are YTE-modified isoforms to extend their half-lives and minimise the potential risk of antibody-dependent enhancement of disease.[16] YTE is a series of three amino acid modifications, namely M252Y/S254T/T256E which is proven to prolong the therapeutic effect of therapeutic antibodies, thereby reducing frequency of administration.[17] Upon administration, tixagevimab and cilgavimab binds simultaneously to non-overlapping regions of the receptor binding domain of the SARS-CoV-2 spike protein. These monoclonal antibodies prevent the SARS-CoV-2 spike protein from binding to the angiotensin-converting enzyme (ACE)-2 receptor, a crucial step for viral attachment.[18,19]

Evidence from Clinical Trials

Pre-Exposure Prophylaxis: PROVENT trial[20]

The PROVENT trial (*n* = 5197) is an ongoing, randomised, double-blind, placebo-controlled trial. Participants were adults (aged 18 or older) who are either at an increased risk of having inadequate response to COVID-19 vaccinations or an increased risk of exposure to SARS-CoV-2. From November 2020 to March 2021, eligible participants were randomised in 2:1 ratio to receive one dose of tixagevimab-cilgavimab (300 mg in total). At baseline, median age of recruited subjects was 53.5 years old, 77.3% of participants were considered by investigators to be at risk for insufficient response to COVID-19 vaccination, and 77.5% had at least one factor for developing severe COVID-19 disease.

The primary efficacy endpoint is symptomatic, reverse transcriptase–polymerase chain reaction (RT-PCR)-confirmed COVID-19 infection (from day of administration till day 183). The primary analysis was conducted with a median follow-up of 83 days. A significantly lower incidence of symptomatic COVID-19 infection is observed among participants who received the monoclonal antibody combination, compared to placebo (0.2% [8/3441] *versus* 1.0% [17/1731], relative risk reduction 76.7%, 95% CI 46.0–90.0%, p <0.001). At an extended follow-up (median follow-up period of 6 months), the relative risk reduction is 82.8% (95% CI 65.8–91.4%), with 11/3441 (0.3%) of subjects in the treatment arm who experienced symptomatic, RT-PCR-confirmed COVID-19 infection and 31/1731 (1.8%) in the placebo arm). The results of this trial suggested that a single dose of tixagevimab-cilgavimab is effective as pre-exposure prophylaxis for COVID-19, with sustained protection at 6 months.

However, since the trial was conducted before the emergence and dominance of the Omicron variant, whether the efficacy shown is preserved against the Omicron strain requires further confirmational studies. In addition, only 3.3% of recruited subjects were receiving immunosuppressive therapy and 0.5% has an immunosuppressive disease. Therefore, the PROVENT trial population may not adequately represent the group of individuals eligible for tixagevimab-cilgavimab under the current emergency use authorisation.

Post-Exposure Prophylaxis: STORM CHASER trial[21]

The STORM CHASER trial (*n* = 1121) is an ongoing randomised, double-blind, placebo-controlled phase III study which evaluated the effect of tixagevimab-cilgavimab in unvaccinated adults who had a potential SARS-CoV-2 exposure recently (within 8 days) to an individual with an antigen test- or RT-PCR-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Participants were randomised in 2:1 ratio to receive one dose of 300 mg tixagevimab-cilgavimab or placebo. The primary efficacy endpoint is symptomatic, RT-PCR-confirmed COVID-19 infection (from day of administration till day 183). The primary analysis was conducted with a median follow-up of 83 days. In the non-peer-reviewed correspondence published by AstraZeneca, they reported that the primary endpoint of post-exposure prophylaxis against symptomatic COVID-19 is not met, as there is a non-significant reduction in risk of developing symptomatic COVID-19 of 33% (95% CI –26 to 65%).

Therefore, tixagevimab-cilgavimab is not authorised for post-exposure prophylaxis of COVID-19.

Early Out-Patient Treatment: TACKLE trial[22]

The TACKLE trial (*n* = 903) is a randomised, double-blind, placebo-controlled phase III study which aims to evaluate the role of tixagevimab-cilgavimab as early out-patient treatment of COVID-19 for unvaccinated individuals i.e. post-exposure prophylaxis. Non-hospitalised patients with a recent (defined as within 3 days before subject recruitment) laboratory-confirmed COVID-19 infection (by RT-PCR or antigen testing) were recruited between Jan 2021 and July 2021. Subjects were randomised in 1:1 ratio to receive one dose of 600 mg tixagevimab-cilgavimab or placebo. At baseline, median age was 45.9 years old and 90% of subjects were considered at high risk of progression to severe COVID-19.

The primary efficacy endpoint of the trial is a composite of either severe COVID-19 (defined as pneumonia or hypoxaemia) or death from any cause from randomisation until day 29. Tixagevimab-cilgavimab reduced development of severe COVID-19 or death by 50% (18/407 [4%] in treatment arm versus 37/415 [9%] in placebo arm, RR reduction 50.5% [95% CI 14.6–71.3%], *p*=0.0096). COVID-19-reported deaths occurred in 3 participants of the treatment arm and 6 participants of the placebo arm. The monoclonal antibody combination provided greatest reduction of risk of severe COVID-19 or death when administered promptly after symptom onset. The relative risk reduction was 88.0% (95% CI 9.4–98.4%) if randomisation occurred ≤3 days of symptom onset, and 50.5% (95% CI 14.6–71.3%) if randomisation occurred ≤7 days of symptom onset. The TACKLE study demonstrated that tixagevimab-cilgavimab may be a convenient out-patient treatment for patients with mild to moderate COVID-19 with recent development of symptoms (≤7 days). Despite promising results from the TACKLE study, the FDA has not approved tixagevimab-cilgavimab for early treatment of COVID-19 in the out-patient setting.

Efficacy in Hospitalised COVID-19 Patients: ACTIV-3-TICO Trial[23]

The ACTIV-3-TICO trial (*n* = 1417) is a randomised, double-blind, placebo-controlled phase III study which aims to evaluate the role of tixagevimab-cilgavimab versus placebo in patients hospitalised with COVID-19 receiving remdesivir. This clinical trial excluded patients with severe COVID-19, as evident from acute organ failure receiving invasive ventilatory or circulatory support, or newly initiated renal replacement therapy. Eligible subjects were randomised in 1:1 ratio to receive either tixagevimab-cilgavimab (300 mg for each component) or placebo. The primary outcome was time to sustained clinical recovery (defined as being discharged from the hospital and staying at home for 14 consecutive days). Sustained recovery was attained by 78% of subjects who received tixagevimab-cilgavimab and 76% of those who received placebo at day 28, and the cumulative incidence was 89% and 86% respectively by day 90 (HR 1.08, 95% CI 0.97–1.20, *p* = 0.21) which suggests that tixagevimab-cilgavimab has no role in improving patient recovery among hospitalised COVID-19 patients. Of note, all-cause mortality till 90 days from randomisation (a secondary outcome in this trial) reached statistical significance. 9% of the tixagevimab-cilgavimab arm (61/710) died at day 90 versus 12% in the placebo arm (86/707) (HR 0.70, 95% 0.50–0.97, *p* = 0.032). The 30% relative risk reduction in mortality among those treated with tixagevimab-cilgavimab sparks discussion on whether it can be used in patients who are hospitalised.[24] At the time of writing, tixagevimab-cilgavimab is not indicated for treatment of COVID-19 and more evidence is needed to support its treatment role in a Omicron-dominating disease landscape (the ACTIV-3-TIGO trial is conducted before the Omicron variant emerged as the dominating variant in circulation).

Efficacy of tixagevimab-cilgavimab in the Omicron era

As pivotal clinical trials on tixagevimab-cilgavimab were conducted before the emergence of the Omicron variant, whether the monoclonal antibodies retain their efficacy against now-prevailing strains of SARS-CoV-2 require additional support from real life evidence and experimental data.

In vitro Studies

The emergence of the Omicron variant has casted doubts on whether tixagevimab-cilgavimab still retains its efficacy against these heavily mutated sub-lineages. Numerous studies evaluated the ability of tixagevimab-cilgavimab in neutralising Omicron variants using live viruses or pseudovirus models. In cell culture, BA.1 subvariant partially evaded binding by both cilgavimab and tixagevimab.[18,25] Cilgavimab neutralised BA.2 subvariant to a greater extent when compared to its ability in neutralising BA.1. Hence, tixagevimab-cilgavimab is expected to retain neutralising activity against BA.2 subvariant.[18,26] The monoclonal antibody combination is expected to be even less effective in neutralising BA.4/5 due to additional mutations hampering the neutralising ability of tixagevimab-cilgavimab.

Real-World Evidence

In an observational, multicentre cohort study conducted in France, 1112 immunocompromised patients were recruited to receive one dose of 300 mg tixagevimab-cilgavimab.[27] All subjects must have received at least 3 doses of COVID-19 vaccine (the type of vaccine received was not reported) and has insufficient vaccine response as shown by insufficient anti-Spike IgG antibodies. The majority of subjects were solid organ transplant recipients, patients with haematological malignancies or patients receiving rituximab therapy for autoimmune conditions. At a median follow-up of 63 days, 56 out of 1112 subjects developed COVID-19 following tixagevimab-cilgavimab, of which 49 had confirmed COVID-19 infection ≥5 days after receiving tixagevimab-cilgavimab. COVID-19 infection by a positive RT-PCR or rapid antigen test using nasal specimens and were self-reported by subjects to their physicians. All cases with variant information were infected by the Omicron variant of SARS-CoV-2. The study was conducted in France between December 2021 and March 2022 during the Omicron surge. The mean weekly incidence rate of COVID-19 was 1669 in 100000 in the population of Ile-de-France and 530 in 100000 among study subjects. While demographic data and vaccination status among the study subjects differ from that of the general public, this study provides early positive data in favour of incorporating pre-exposure prophylaxis with tixagevimab-cilgavimab as part of the COVID-19 prevention strategy.

Another group of researchers from the United States conducted a retrospective cohort study to compare the development of breakthrough SARS-CoV-2 infection among 222 solid organ transplant recipients who received tixagevimab-cilgavimab when compared to the control arm which consists of vaccine-matched solid organ transplant recipients.[28] At a mean follow-up of 87 days, a lower incidence of COVID-19 in the treatment arm was noted (11/222 [5%] in treatment arm versus 32/222 [14%] in control arm, p <0.001). Numerically, the number of patients who received tixagevimab-cilgavimab and hospitalised for COVID-19 is lower than that for the control arm (1/222 versus 6/222). This study was conducted during the Omicron phase of the pandemic (precisely when BA.1, BA.2 subvariants were most detected), but before the circulation of BA.4 and BA.5 subvariants. Therefore, it is still unsure whether the protection offered by the monoclonal antibody cocktail could translate to clinical efficacy when the dominating subvariant is BA.4/5.

Approved Indication and Eligibility

Tixagevimab-cilgavimab is indicated for individuals ≥12 years old with body weight of ≥40 kg meeting one of the following criteria:

- Moderate to severe immune compromise due to a medical condition, or
- Currently taking immunosuppressants and may not mount an adequate response to COVID-19 vaccinations
- History of severe adverse reaction to a COVID-19 vaccine or its components

Patients with an active SARS-CoV-2 infection or in recent contact with an individual with SARS-CoV-2 infection should not receive tixagevimab-cilgavimab as it is not authorised for post-exposure prophylaxis (PEP).[29]

According to the Emergency Use Authorisation, individuals satisfying the following conditions are considered to be moderately or severely immunocompromised:[18,30]

- Receiving active treatment for solid tumours and haematologic malignancies
- Organ transplant recipient on immunosuppressants
- Chimeric antigen receptor (CAR)-T-cell therapy or stem cell transplant recipient (within the last 2 years)
- Moderate or severe primary immunodeficiency e.g. DiGeorge syndrome, Wiskott-Aldrich syndrome
- Advanced or untreated HIV infection (people with HIV and CD4 T lymphocyte counts <200 cells/mm^3, a history of AIDS-defining illness or symptomatic HIV)
- Active treatment with high-dose corticosteroids (equivalent to ≥20 mg prednisolone per day for ≥2 weeks), chemotherapy, immunosuppressants, B cell-depleting agents etc.

Dosage and Administration (Including Post-EUA Revisions)

On February 24, 2022, the FDA revised the dosage of tixagevimab-cilgavimab due to more recent data suggesting attenuated effect of the agents against recently dominating subvariants of COVID-19.[31] As at November 2022, the Hospital Authority Factsheet on Evusheld recommends the dose of tixagevimab-cilgavimab (i.e. 600 mg in total).[32] The initial dose of tixagevimab-cilgavimab in patients ≥12 years old weighing ≥40 kg is 300 mg of tixagevimab and 300

mg of cilgavimab given as two separate, consecutive intramuscular injections. This is an updated dosing regimen because of *in vitro* data suggesting attenuated effect of the monoclonal antibodies against omicron BA.1 and BA.1.1 (BA.1 + R346K mutation) subvariants.[18,30,33]

As a lower dose of tixagevimab-cilgavimab was initially authorised (single dose of 150 mg of tixagevimab and 150 mg of cilgavimab), individuals who received the lower initial dose should receive an additional make-up dose. If the initial dose is given more than 3 months ago, the patient should receive a full dose (300 mg of each monoclonal antibody) again. If the initial dose is administered within the past 3 months, a make-up dose of 150 mg of each component should be given.[18]

Repeated dosing is now permitted based on the revised EUA. On June 29, 2022, the FDA updated their recommendations on the frequency of administrating tixagevimab-cilgavimab in eligible individuals. They now recommend repeated dosing of 300 mg of tixagevimab and 300 mg of cilgavimab every 6 months if sustained protection is considered necessary.[31] Repeated dosing can be administered 6 months from the date of the latest injection.[18]

For individuals who recently received a dose of COVID-19 vaccine, tixagevimab-cilgavimab should be administered at least two weeks after vaccination.[18]

Pharmacokinetics

The elimination half-life is 87.9 ± 13.9 days and 82.9 ± 12.3 days for tixagevimab and cilgavimab respectively. The time to peak is 14.9 and 15.0 days for tixagevimab and cilgavimab respectively.[18] Both monoclonal antibodies are not eliminated intact in the urine.[18]

Adverse Drug Effects

Tixagevimab-cilgavimab is well-tolerated in clinical trials. In the PROVENT study (which used the initially authorised lower dose of tixagevimab-cilgavimab), adverse events were reported in 1221/3461 (35.3%) in the tixagevimab-cilgavimab arm, with only 1.8% classified as severe adverse events.[20] The proportion of subjects who experienced adverse events in the treatment arm is similar to that in the placebo arm, with 593/1736 (34.2%) subjects who reported adverse events, of which 1.6% were severe. Proportion of subjects who developed an injection-site reaction is similar across arms (2.4% *versus* 2.1% in the treatment and placebo arms respectively). The most common adverse events (which occurred in ≥3% of subjects) were headache, fatigue and cough.[18]

In the TACKLE trial (which used the higher dose of tixagevimab-cilgavimab), adverse events were reported by 132/452 (29%) of subjects in the treatment arm and 163/451 (36%) in the placebo arm. The majority of adverse events were mild to moderate in severity.[22]

Cardiovascular Adverse Events

In the PROVENT trial, cardiac serious adverse events (SAEs) were reported by 22/3461 (0.6%) of subjects in the treatment arm and 3/1736 (0.2%) of the placebo arm. In the TACKLE trial, cardiac SAEs were reported in 3 subjects who received tixagevimab-cilgavimab (2 cases of acute myocardial infarction and 1 case of sudden cardiac death) and 1 subject who received placebo (who reported arrhythmias). All subjects who experienced cardiac SAEs had cardiac risk factors and / or past history of cardiovascular disease at baseline.[22] Therefore, prescribers should weigh the risks and benefits prior to administering tixagevimab-cilgavimab to individuals at high risk for cardiovascular events. Recipients should monitor for signs and symptoms that are suggestive of a cardiovascular event.[18]

CONCLUSION

Currently, tixagevimab-cilgavimab is the only safe and effective option for pre-exposure prophylaxis for patients expected to have an insufficient immune response to vaccination against COVID-19. With limited efficacy data available for the revised dose (300 mg of tixagevimab and 300 mg of cilgavimab) in preventing COVID-19 infections which are primarily caused by Omicron variants BA.4/5 in the recent months, recipients of tixagevimab-cilgavimab should still practice personal hygiene and general prevention measures.

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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

COVID-19: Update on Evidence for a Pre-Exposure Prophylaxis Strategy versus Post-Exposure Prophylaxis

1. ***As at 13 August 2022, which of the following is considered to be a SARS-CoV-2 variant of concern by the U.S. government?***
   A. Alpha
   B. Beta
   C. Delta
   D. Omicron

2. ***Tixagevimab-cilgavimab is granted an emergency use authorisation for which of the following indications?***
   A. Pre-exposure prophylaxis of COVID-19
   B. Post-exposure prophylaxis of COVID-19
   C. Treatment of mild-to-moderate COVID-19
   D. Treatment of severe COVID-19

3. ***Which of the following monoclonal antibody regimen(s) was / were studied as potential pre-exposure prophylaxis option(s) in clinical trial setting before the emergence of the Omicron variant?***
   A. Bamlanivimab
   B. Casirivimab-imdevimab
   C. Sotrovimab
   D. A and B

4. ***Which of the following is FALSE regarding the mechanism of action of tixagevimab-cilgavimab?***
   A. Both tixagevimab and cilgavimab are recombinant monoclonal antibodies.
   B. Tixagevimab and cilgavimab has modified amino acid sequences to prolong their half-lives.
   C. Tixagevimab binds to the SARS-CoV-2 spike protein, whereas cilgavimab binds to the ACE-2 receptor on host cells.
   D. None of the above.

5. ***Which of the following is true regarding clinical trials on tixagevimab-cilgavimab?***
   A. The PROVENT trial was conducted during the surge of Omicron variant, thus providing valuable evidence in favour of the use of tixagevimab-cilgavimab when Omicron is the dominating SARS-CoV-2 strain circulating globally.
   B. The STORM CHASER trial demonstrated significant reduction in symptomatic COVID-19 infection when tixagevimab-cilgavimab is given after an individual had high-risk exposure.
   C. Results of the TACKLE trial suggested that tixagevimab-cilgavimab may be used as early out-patient treatment of mild-to-moderate COVID-19 among those with recent onset of symptoms.
   D. The ACTIV-3-TICO trial recruited solely patients with severe COVID-19 receiving ventilatory support, and concluded that tixagevimab-cilgavimab should be administered to this population.

6. ***Which of the following individuals are eligible for tixagevimab-cilgavimab therapy?***
   A. A 8-year-old boy with documented anaphylactic reaction to Comirnaty vaccine.
   B. A 30-year-old female who received haematological stem cell transplant 3 years ago.
   C. A 59-year-old male who is started on oral prednisolone 50 mg once daily for 5 days for acute exacerbation of asthma.
   D. A 72-year-old female who is receiving obinutuzumab and venetoclax for chronic lymphocytic leukaemia.

7. ***Which of the following regarding the dosing recommendations of tixagevimab-cilgavimab is true?***
   A. If sustained protection against COVID-19 is deemed necessary, tixagevimab-cilgavimab can be given every 12 weeks.
   B. An individual who received 150 mg of tixagevimab and 150 mg cilgavimab 2 months ago should receive an additional dose of 300 mg of tixagevimab and 300 mg cilgavimab to strengthen protection against highly mutated Omicron variants.
   C. An individual who received 150 mg of tixagevimab and 150 mg cilgavimab 4 months ago should receive an additional dose of 300 mg of tixagevimab and 300 mg cilgavimab to strengthen protection against highly mutated Omicron variants.
   D. The injections of tixagevimab and cilgavimab should be given at least 5 days apart.

8. ***A patient just received a dose of the Comirnaty vaccine today. According to FDA's recommendation, when earliest can he / she receive a dose of tixagevimab-cilgavimab?***
   A. 1 week after vaccination
   B. 2 weeks after vaccination
   C. 3 weeks after vaccination
   D. 4 weeks after vaccination

9. ***Which of the following is false regarding the adverse events of tixagevimab-cilgavimab?***
   A. Common adverse events of tixagevimab-cilgavimab include headache, fatigue and cough.
   B. Bradycardia is commonly associated with tixagevimab-cilgavimab and thus patients should be monitored on site for at least 1 hour after they receive the injections.
   C. Tixagevimab-cilgavimab is well tolerated and the majority of adverse events reported were mild to moderate in severity.
   D. None of the above.

10. ***Which of the following is true regarding the use of tixagevimab-cilgavimab in patients with cardiovascular diseases?***
    A. Tixagevimab-cilgavimab should never be administered to a patient with past history of arrhythmia or heart failure.
    B. In both the PROVENT and TACKLE trials, cardiac serious adverse events were significantly greater in subjects who received tixagevimab-cilgavimab compared to subjects who received placebo.
    C. Physicians should weigh the risk and benefits of initiating tixagevimab-cilgavimab in patients with a history of cardiovascular disorders.
    D. None of the above.

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 292(D&T)

Management of Hospital-acquired Pneumonia and Ventilator-associated Pneumonia: The Conventional and Novel Antimicrobials

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

Awareness and Knowledge on Atrial Fibrillation and Oral Anticoagulants of Patients in Hong Kong

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ABSTRACT

This study evaluated the knowledge about AF and oral anticoagulants (OAC) of the patients attending SOPC at PWH. The preference for new oral anticoagulants (NOAC) in warfarin users and patients' willingness to be involved in disease management are also examined. A survey-based study was conducted between January and March 2016 in the form of on-site interview and telephone survey.

309 patients completed the survey. 89% of respondents had never heard of AF, and there was no significant difference between the knowledge of AF subjects and non-AF subjects. Suboptimal knowledge about warfarin was found, and only 15.6% of patients knew their target INR. 40% of warfarin users were willing to switch to NOAC after being told the advantages, but the number dropped to 7% when the price of NOAC was disclosed. In the question which assumes patient having AF, 27% of non-AF subjects refused to take OAC to reduce the risk of stroke because of the bleeding risk. In the AF subject group, 55% of patients expressed willingness to continue to take OAC given that it reduces the risk of stroke by 60-70% despite the small (1-2%) risk of severe bleeding. Patients had inadequate knowledge about AF and OAC, and drug cost was a major factor affecting the choice of OAC in the study population. Furthermore, patients had a passive role in the decision-making process of their disease management.

Keywords: *Atrial fibrillation, Oral Anticoagulants, Awareness, Knowledge*

INTRODUCTION

Atrial fibrillation (AF), which is the most common type of arrhythmia, significantly increases the risk of stroke by 5 times.(1) Unfortunately, AF can be asymptomatic,(2) and many patients could only find out that they have AF after they have an episode of stroke. Therefore, the early detection of AF is crucial. Inspired by two local studies investigating the impact of pharmacy outreach services on AF knowledge and management,(3,4) this study also adopted AliveCor (AliveCor Inc., San Francisco, California, USA) as a fast-screening tool for AF, which is an iPhone-based handheld device for generating a one-lead electrocardiogram (ECG) in 30 seconds. When compared to the conventional 12-lead ECG, AliveCor is more convenient, but less costly and time-consuming.

The knowledge about AF is poor in the general elderly population of Hong Kong, and less than 8% of the elderly have ever heard of AF.(3) Nevertheless, the awareness towards AF is also low among the AF population. A survey-based study in UK revealed that less than half of the AF patients could name their cardiac condition, and over 40% of them thought that AF is not a serious disease.(5) In view of this, this study investigated the knowledge about AF of patients in the specialized out-patient clinic (SOPC) at Prince of Wales Hospital (PWH), who had a higher baseline risk of heart diseases and were supposed to have a better understanding about AF when compared to the general elderly population.

After the diagnosis of AF, early initiation of anticoagulants is recommended for patients with CHA_2DS_2-VASc score > 2 to reduce the risk of stroke.(2) Warfarin is the most common drug of choice, but it is associated with a lot of interactions with other drugs and food. Frequent monitoring of international normalized ratio (INR) is also required because of the narrow therapeutic range of warfarin. As a result, patients' compliance and drug knowledge are important. Novel oral anticoagulants (NOAC) are convenient choices which have fewer drug interactions and do not require frequent monitoring. However, they are more expensive and not all patients are willing to pay for that. Therefore, this study aimed to assess AF patients' knowledge about OAC and their preference for NOAC. The primary objective of this study was to evaluate the awareness and knowledge about AF of patients in specialized out-patient clinic (SOPC) at PWH. The secondary objective of this study was

to assess the knowledge of patients about their oral anticoagulants and disease management. This study also examined patient's preference for NOAC.

METHODS

This study targeted at elderly patients who have follow-up consultations at SOPC of PWH, including cardiology clinic, geriatric clinic, hypertension clinic, warfarin clinic, lipid clinic and family medicine clinic. These patients were selected because they had underlying cardiovascular diseases, and they had a higher risk of developing AF. Patients aged 65 years old or above and had follow-up appointments at the designated SOPC of PWH were recruited. Patients who failed to respond to the questionnaire due to hearing disorders or cognitive problems and who could not generate an ECG with AliveCor because of movement, muscle tremor, hemiplegia or poor contact surface with the electrode were excluded.

This was a survey-based study investigating patients' knowledge about AF and OAC. A questionnaire was tailor designed for this purpose. The survey was conducted in two methods, including on-site interview and telephone survey. On-site interview was carried out during January to March 2016. Patients at the waiting area on the first floor of Li Ka Shing Specialist Clinic at PWH were invited to undergo AF screening with AliveCor based on convenience sampling. Patients were asked to present their appointment slip in advance to check if they satisfy the inclusion criteria. After the rapid screening with AliveCor, a survey was conducted to assess patients' knowledge about AF. The results of AliveCor were reviewed by cardiologist, and would not be discussed in this study. Demographic information of patients was obtained through Clinical Management System (CMS) of PWH. Their age, current OAC therapy, total number of medications, history of stroke, TIA or thromboembolism, bleeding history and disease state were recorded.

The questionnaire used in this study was adapted from a local study about impact of pharmacy outreach service on AF knowledge of the elderly population.[3] The questionnaire was reviewed by cardiologist. The questionnaire consisted of 28 questions. Question 1 – 9 gauged patients' awareness and knowledge about AF. Question 10 – 14 were designed to evaluate patients' general understanding about OAC. Questions 15 – 21 were only applicable to patients currently on warfarin, and their knowledge about drug usage, monitoring and NOAC were examined. Questions 22 – 23 only applied to patients currently on NOAC. Questions 24 – 26 were intended to understand patients' preference for NOAC. All patients were required to answer questions 27 – 28, which assessed patients' opinion on the disease management of AF.

Statistical analysis

Microsoft Excel 2010 and IBM SPSS Statistics 22 were adopted for statistical analysis in this study. The level of significance was 0.05. The demographic information of AF patients and non-AF patients were compared using independent sample t test, Chi-square test and Fisher's exact test. Multiple linear regression was utilized to look for correlation between AF knowledge and different variables. Multiple linear regression was also applied in the analysis of factors affecting patients' willingness to take OAC.

RESULTS

Three hundred and nine patients were recruited in this study. Patients were categorized into two groups, namely AF subjects and "non-AF" subject, according to their AF status. The "non-AF" group also included patients with arrhythmia other than AF and patients with previously unknown AF (i.e. they were newly found to have AF during this screening project), assuming that they had the same baseline knowledge about AF as those without AF **(Table 1)**.

The mean age of this study population was 77.7 ± 7.4 years old. In the AF group, 51.2% patients were on warfarin, 15.9% were on dabigatran, 20% were on rivaroxaban and 1.8% were on apixaban. In the "non-AF" group, the majority (96.4%) of patients were not on any OAC. There were statistical differences between the total number of medications and stroke history of two groups **(Table 1)**. Patients with known AF were asked about their perception of their own conditions (n=170). Patients with previously unknown AF were excluded in this question. 46% of the respondents were not aware that they have the disease, and only 7% of them could accurately tell that they have AF. Patient's AF knowledge with respect to each item in the assessment scheme is summarized in **Table 2**. 89% of the respondents had never heard of AF, and only 2.6% of them could correctly tell the complications of AF. The perceived severity of AF was 4.16 out of 5, which indicates that respondents did think that AF is a serious disease. Nevertheless, it is noteworthy that merely 25 patients responded to this question. Only about 6% of them knew that AF can be asymptomatic, and symptoms could come and go. Slightly more respondents (about 9%) were aware that people with advanced age and underlying heart diseases are at higher risk of developing AF **(Table 2)**.

DISCUSSION

It was assumed that AF Knowledge in the AF group would be better than that of non-AF group. Nevertheless, results did not demonstrate statistical difference between the knowledge of two groups. Even worse, 45% of patients with arrhythmia failed to notice their heart problems.

Table 1. Patients' Demographics				
Characteristics	**All subjects (n=309)**	**AF subjects (n=170)**	**"Non-AF" subjects (n=139)**	**p-value#**
Gender, n (%)				0.363 [a]
Male	160 (51.8)	92 (54.1)	68 (48,9)	
Female	149 (48.2)	78 (45.9)	71 (51.1)	
Mean age (SD)	77.7 ± 7.4	78.0 ± 6.8	77.4 ± 8.0	0.497 [b]
Current OAC therapy, n (%)				
Warfarin	90 (29.1)	87 (51.2)	3 (2.2)	<0.001 [c]
Dabigatran	27 (8.7)	27 (15.9)	0 (0)	<0.001 [c]
Rivaroxaban	35 (11.3)	34 (20)	1 (0.7)	<0.001 [c]
Apixaban	4 (1.3)	3 (1.8)	1 (0.7)	0.630 [c]
Not on any OAC	153 (49.5)	19 (11.2)	134 (96.4)	<0.001 [a]
Mean of total number of medications (SD)	8.62 ± 4.4	9.1 ± 4.6	8.0 ± 4.2	0.022 [b]
Have a history of stroke, TIA or thromboembolism, n (%)	100 (32.4)	67 (39.4)	33 (23.7)	0.003 [c]
Disease state, n (%)				
Known AF	165 (53.4)	165 (97.1)		-
Known pAF	5 (1.6)	5 (2.9)		-
Known atrial flutter	2 (0.6)		2 (1.4)	-
Other arrhythmia	2 (0.6)		2 (1.4)	-
Previously unknown AF	13 (4.2)		13 (9.4)	-
No known AF or arrhythmia	122 (39.5)		122 (87.8)	-

Abbreviations: AF, atrial fibrillation; pAF, paroxysmal atrial fibrillation; OAC, oral anticoagulant; TIA, transient ischemic attack; SD, standard deviation.
p-value compares AF subjects vs. "non-AF" subjects
[a] p-value calculated by Chi-square test
[b] p-value calculated by Independent sample t test
[c] p-value calculated by Fisher's exact test

Table 2. Patients' knowledge about AF					
Item		**All subjects (n=309)**	**AF subjects (n=170)**	**"Non-AF" subjects (n=139)**	**p-value**
1	**Yes**	34 (11.0%)	22 (12.9%)	12 (8.6%)	0.229 [a]
	No	275 (89.0%)	148 (87.1%)	127 (91.4%)	
2*	**Perceived severity**	4.16 ± 1.2 (n=25)	3.87 ± 1.4 (n=15)	4.6 ± 0.7 (n=10)	0.142 [b]
3	**Answered correctly**	8 (2.6%)	5 (2.9%)	3 (2.2%)	0.734 [c]
4	**Aware**	19 (6.1%)	10 (5.9%)	9 (6.5%)	0.829 [a]
	Not aware	290 (93.9%)	160 (94.1%)	130 (93.5%)	
5	**Aware**	21 (6.8%)	12 (7.1%)	9 (6.5%)	0.839 [a]
	Not aware	288 (93.2%)	158 (92.9%)	130 (93.5%)	
6	**Aware**	19 (6.1%)	10 (5.9%)	9 (6.5%)	0.829 [a]
	Not aware	290 (93.9%)	160 (94.1%)	130 (93.5%)	
7	**Aware**	27 (8.7%)	17 (10%)	10 (7.2%)	0.385 [a]
	Not aware	282 (91.3%)	153 (90%)	129 (92.8%)	
8	**Aware**	28 (9.1%)	17 (10%)	11 (7.9%)	0.525 [a]
	Not aware	281 (90.9%)	153 (90%)	128 (92.1%)	

* some patients were excluded because they answered "don't know"
[a] p-value calculated by Chi-square test
[b] p-value calculated by Independent sample t test
[c] p-value calculated by Fisher's exact test

Comparison with other similar studies

This study showed similar results with other local studies. About 11% of respondents have heard of AF, while a local study in 2015 revealed that about 7.7% of the community elderly population have heard of AF.[3] The population of this study might be slightly more aware of AF because they have more frequent follow-up consultations at SOPC, and they have other underlying cardiovascular problems, which alert them to other heart diseases.

However, the results of this study were somewhat different from studies of other countries. In this study only 5.9% of AF patients were aware that AF can increase the risk of stroke by 5 times. On the other hand, a survey-based study in UK demonstrated that 54% of AF patients were aware that AF predisposes to stroke, and 80% understood that AF is cardiac rhythm abnormality.[5] A similar study in the US also illustrated that 46% of patients with recently detected AF were able to identify AF as a risk of stroke.[6] This study revealed poor knowledge of AF patients in Hong Kong. First of all, there is a lack of health education about AF despite its seriousness. Secondly, the concept of AF is rather complex, and the Chinese translation of AF, "心房顫動", can be quite difficult for elderly patients

to understand. These can hinder patients' understanding of AF. Furthermore, public hospitals are overloaded, and physicians only have limited time for each patient. They may not have enough time to explain to patients about their conditions thoroughly.

Aspirin is an antiplatelet drug, and it is well known to be inferior to OAC in stroke prevention in AF patients. However, misconceptions about aspirin are common. In this study, more than 26% of patients who were not on OAC mistook aspirin for OAC. They could not distinguish antiplatelet drugs from anticoagulants. Most respondents understood that OAC can thin blood, but only 61.5% were aware that OAC is for stroke prevention. In addition, almost 35% did not know that OAC can increase bleeding risk. Their lack of knowledge about OAC may put them at risk, as they did not adopt adequate measures to prevent accidental bleeding. They may not be aware of the signs of severe bleeding so as to notify the doctor or seek help timely.

Due to limited time and resources, only 309 patients were successfully reached. Among the study population, only 90 patients were on warfarin, and therefore the sample size for questions regarding warfarin knowledge and preference for NOAC was rather small. Since we would like to recruit more patients within limited period of time, both telephone survey and on-site interview were conducted. Patients surveyed through different methods might have different perceptions on disease management and screening. Besides, this study evaluated patients' knowledge about AF, which was self-reported by patients. For questions asking preferences and opinions, patients might interpret the scale differently. Lastly, the survey was not formally validated. However, the survey was adapted from previous local studies,[3, 4] and the questions were tailored for the elderly population in Hong Kong and reviewed by physician.

CONCLUSION

There was a universally low awareness about AF, and only 11% of patients had ever heard of AF. Patients lacked general understanding about OAC, and they also had suboptimal knowledge about warfarin. Moreover, this study suggested that drug cost is an important factor for patients when choosing anticoagulants.

In terms of disease management, not all patients were willing to take OAC if diagnosed with AF because of the bleeding risk. A minority of patients (11%) showed reluctance to disease screening. Generally, this study demonstrated that patients were passive in the decision making process of disease management as quite a few patients answered "don't know" or "let the doctor decide" in questions asking about their preference in choosing OAC or initiation of therapy. Patients should be better educated about AF and the importance of initiating anticoagulation therapy. Pharmacists, who are drug experts, can spend more time in medication counselling and expand warfarin clinic so that more patients could be benefited. Leaflets and posters are also good tools for educating patients about signs of AF and stroke. The idea of self-care should be promoted as well to advocate the active participation of patients in disease management.

Conflict of Interest:

All authors declared that there was no conflict of interest during the study and the preparation of the manuscript.

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The Activities of the Pharmaceutical Society of Hong Kong

2022-23 General Council of Pharmaceutical Society of Hong Kong and Pharmaceutical Society Charitable Foundation Limited

We are pleased to announce that the Annual General Meeting of The Pharmaceutical Society of Hong Kong (PSHK) and The Pharmaceutical Society Charitable Foundation Limited (PSCF) has been held at PSHK Clubhouse on 15th December 2022. The following members were elected for the tenure from 15th December, 2022 onwards for 2022-2023 term.

President:	Mr. Dick SUNG
Vice-presidents:	Ms. Beverley TAM Mr. Edward YAU
Hon. Secretary:	Mr. Jonathan NG
Hon. Treasurer:	Mr. Paul LAM
Council Members:	Mr. Philip CHAN Mr. CHEUNG Wai Keung Mr. Ian CHEUNG Ms. Kathleen KUNG Mr. Vincent LAU Mr. Raymond LUK Mr. Rex NG Mr. Patrick TAM Ms. Sandra TSANG Ms. Tina YAP
Pharmacy & Poisons Board Members:	Mr. Dick SUNG Ms. Beverley TAM Ms. Sandra TSANG

Social event joined in 2022

With the loosening Covid-19 restriction in the second half of 2022, PSHK joined some events to provide free services to public.

大灣區社區醫療健康關愛行動

PSHK joined the event organised by Sum Yee on November 2022. PSHK pharmacists' volunteers provided free medication reconciliation to the citizens.

Photo 1 & 2. *PSHK pharmacists' volunteers.*

九龍城醫護同心顯關懷2022

PSHK was invited to join the event "九龍城醫護同心顯關懷2022" on 3rd-4th December 2022. This social event was organised by Building Healthy Kowloon City Association Limited and co-organised by Home Affairs Department Kowloon City District Office. As one of the supporting organisations, PSHK's pharmacist members provided volunteer medication screening and medication reconciliation for elderly who lived in Kowloon City District.

Photo 3. *Pharmacists were providing medication screening services for elderly.*

Photo 4. *Group photo of pharmacist volunteers*

As the government further relaxed the social distancing measures with the continuing stablised epidemic trend, PSHK hopes to organize more events and provide more free services to public to promote the profession. Please stay tuned for more news from us!

The Activities of the Society of Hospital Pharmacists

SHPHK – 2022 Year End Wrap Up

As the COVID-19 pandemic situation in Hong Kong starts to subside, it is expected that the Hong Kong Government will further relax the existing anti-pandemic measures. The Society of Hospital Pharmacists of Hong Kong (SHPHK) will try and resume organising physical events in 2023 if possible, hoping to better connect Members through different events.

In November 2022, SHPHK conducted a survey to explore the views of Pharmacists, Pharmacy Interns and students on the activity programme of SHPHK and their expectation for the Society. The General Committee Members of SHPHK have listened closely to your views! We will continue to improve in order to encourage a better future for Hong Kong Pharmacists.

Activities Highlights: October - December 2022

HIV Education Campaign 2022

SHPHK has launched an HIV Education Campaign in Q3 aiming to raise public awareness about HIV prevention and treatments. For this campaign, SHPHK has invited different doctors and pharmacists who are specialised in infectious disease to help in producing a video series on HIV/AIDS. The videos have now been uploaded to the SHPHK facebook page (@SHPHK) and the Drug Education Resources Centre (DERC) Website (www.derc.org.hk > 藥物視頻 > 愛滋病資訊頻道) .

Education Video on '愛滋病藥物知多啲' – Ms. Christy Ng, General Committee Member of SHPHK

SHPHK Press Conferences

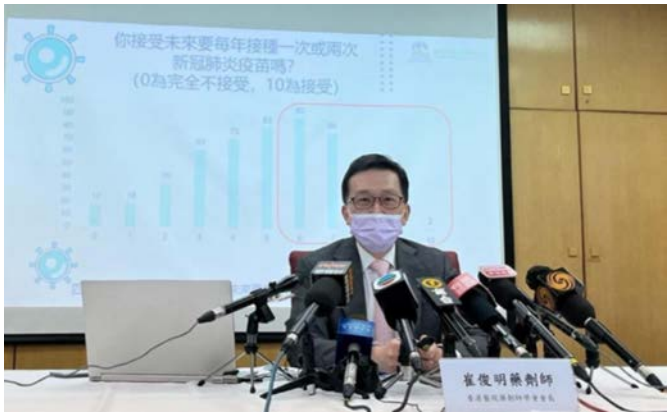
(a) Press Conference on Flu Vaccination 2022-23

An SHPHK press conference regarding the use of intranasal flu vaccines at schools was held on 25th September 2022. The aim of this press conference is to raise public awareness of the COVID-19-influenza double epidemic that may happen in this winter. The best way to prepare for the outbreak is to get vaccinated against both COVID-19 and influenza. If you still have not received the COVID-19 or flu vaccination yet, we would like to take this opportunity to once again encourage you to get vaccinated as soon as possible. Don't forget to encourage your family members, friends and colleagues to get vaccinated too!

SHPHK press conference regarding Influenza Vaccines on 25th September 2022 – Group photo.

(b) Press Conference on the COVID-19 Vaccine Second Booster Dose

Another SHPHK press conference regarding the 4th dose of COVID-19 vaccine was successfully held on 9th October 2022. In this press conference, the Society announced the results of a survey that was previously conducted in September 2022 on the public's attitude towards the COVID-19 vaccine second booster dose in Hong Kong. Mr. William Chui, President of SHPHK highlighted the importance of receiving the fourth dose of the COVID-19 vaccine to avoid the resurgence of COVID-19 in winter.



SHPHK press conference regarding COVID-19 Vaccines on 9th October 2022 – Mr. William Chui, President of SHPHK.

Webinar on Update on Heart Failure Management

On 4th November 2022, SHPHK invited Dr. Catherine Shea, Associate Consultant of Queen Mary Hospital and Ms. Selina Leung, Pharmacist of SHPHK to share with our Members the latest guideline and treatments for heart failure, as well as some practical tips regarding heart failure treatment initiation and titration. The Society would like to thank Dr. Shea and Selina for sparing their time to join us for the session despite their busy schedule, and Mr. Bryan Wong, General Committee Member of SHPHK for chairing the webinar.

SHPHK Webinar on Update on Heart Failure Management on 4th November 2022.

SHPHK Activities: 2022 In Review

February	1. 網上講座: 兒童及青少年注射新冠疫苗
	2. Webinar: 5 -11 Age Group Specific COVID-19 Vaccination Clinical Lead Sharing - How to Remove Air Bubble(s) During Vaccine Preparation (co-organised with Hong Kong Society for Immunisations and Travel Medicines)
April	3. Webinar (for Pharmacists): Clinical Consideration of Using Oral Antiviral Therapy for Symptomatic Mild to Moderate COVID-19 Cases
	4. Webinar (for Nurses): Clinical Considerations of Using Oral Antiviral Therapy for Symptomatic Mild to Moderate COVID-19 Cases
May	5. Webinar (for Dispensers): Clinical Considerations of Using Oral Antiviral Therapy for Symptomatic Mild to Moderate COVID-19 Cases
July	6. Webinar: Introducing Personalised - Cardiovascular Disease Risk Assessment for Chinese (P-CARDIAC)
	7. The 35th SHPHK Annual General Meeting
	8. Webinar: COVID-19 Pre-Exposure Prophylaxis for Immunocompromised Patients
August	9. 網上講座#1:「預防流感上一課：兒童疫苗選擇知多啲」
	10. 網上講座#2:「預防流感上一課：兒童疫苗選擇知多啲」
	11. 網上講座#3:「預防流感上一課：兒童疫苗選擇知多啲」
September	12. Online Training: COVID-19 Info Hub for Healthcare Professionals (co-organised with The University of Hong Kong)
	13. 網上講座#4:「預防流感上一課：兒童疫苗選擇知多啲」
	14. 網上講座#5:「預防流感上一課：兒童疫苗選擇知多啲」
October	15. Webinar: The Clinical Use of Tixagevimab/ Cilgavimab in COVID-19 Pre-exposure Prophylaxis and Treatment
November	16. Webinar: Update on Heart Failure Management
December	17. Webinar: The Roles of Paediatric Pharmacist and Independent Prescriber in the U.K. (co-organised with College of Pharmacy Practice)
Coming in 2023! (TBC)	- SHPHK Webinar on ambulatory care / psychiatry / skin care / gene therapy / radio-ligand therapy…etc. - Hong Kong Pharmacy Conference 2023 - Hiking / Dinner / Movie night…etc. - …..and more!

SHPHK Membership Renewal

Please note that Members will receive a reminder email from SHPHK very soon if their membership is due to renew. Please make sure your membership with SHPHK is up-to-dated so that you could continue to get free access to SHPHK online resources and join the Society's activities for free in 2023!

The General Committee Members of SHPHK would like to take this opportunity to thank all SHPHK Members for their support throughout the year. We wish you all a Merry Christmas and a prosperous year ahead!

You are most welcome to follow the Society's Facebook page (**@SHPHK**) and the SHPHK Instagram (**@shphk1987**) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

edited by Lucilla Leung

Active Ingredients
Upadacitinib

Pharmacological Properties

Indications
As monotherapy or in combination w/ MTX for the treatment of moderate to severe active RA in adults w/ inadequate response to, or w/ intolerance to, ≥1 DMARDs. As monotherapy or in combination w/ MTX for the treatment of active psoriatic arthritis in adults w/ inadequate response to, or w/ intolerance to, ≥1 DMARDs. Treatment of active ankylosing spondylitis in adults w/ inadequate response to conventional therapy. Treatment of moderate to severe atopic dermatitis in adults & adolescents ≥12 yr who are candidates for systemic therapy.

Dosage Forms and Strengths
Each tablets contains 15mg upadacitinib in prolonged release formulation.
Each tablets contains 30mg upadacitinib in prolonged release formulation.

Administration
May be taken with or without food: Swallow whole, do not split or crush or chew.
Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis Adult 15 mg once daily.
Atopic dermatitis Adult 15 or 30 mg once daily. A dose of 30 mg once daily may be appropriate for patients w/ high disease burden or patients w/ inadequate response to 15 mg once daily.
Consider lowest effective dose for maintenance.
Adolescent 12- 17 year, weighing at least 30 kg 15 mg once daily.
Elderly ≥65 year 15 mg once daily.

Contraindications
Hypersensitivity to the active ingredients and to any of the excipients.
Active TB or serious infections.
Severe hepatic impairment.
Pregnancy.

Interactions
Risk of additive immunosuppression with other potent immunosuppressants eg, azathioprine, ciclosporin, tacrolimus & biologic DMARDs or other Janus kinase inhibitors.

Adverse Reactions
Upper Respiratory Tract Infection, acne; bronchitis, herpes zoster, herpes simplex, folliculitis, flu; anaemia, neutropaenia; hypercholesterolaemia;

Dosage Available
Rinvoq Prolonged-Release Tablets 15mg in the pack of 28's.
Rinvoq Prolonged-Release Tablets 30mg in the pack of 28's.

Forensic classification
P1S1S3

Verzenio: The first and only CDK4 & 6 inhibitor to significantly reduce risk of recurrence in combination with ET[1,3]

In patients with HR+, HER2-, node-positive EBC at high risk of recurrence

monarchE enrolled 5,637 node-positive patients with a range of familiar high-risk disease characteristics[1,2]

KEY INCLUSION CRITERIA[1,2]

1 TO 3 POSITIVE NODES

AND

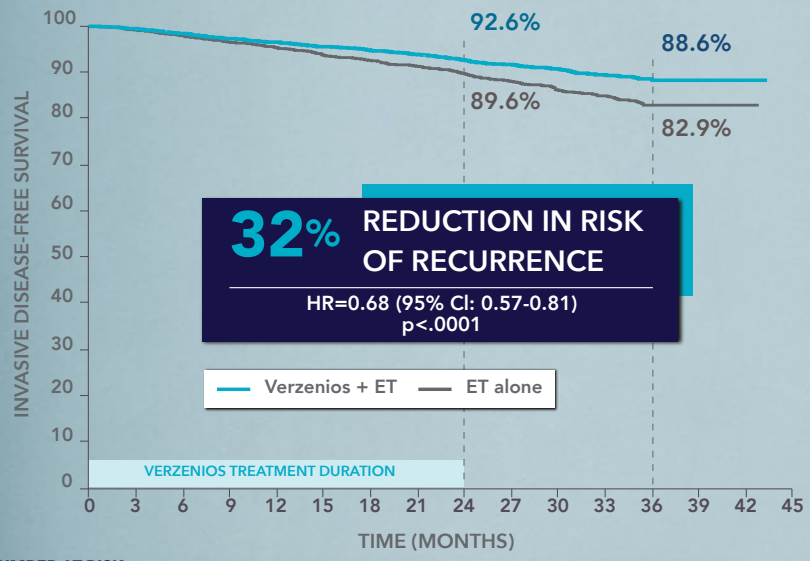
At least one of the following characteristics associated with high risk of recurrence:

- Tumor size ≥5 cm
- Histologic Grade 3

OR

4+ POSITIVE NODES

IDFS IN COHORT 1 POPULATION[1,4]



NUMBER AT RISK

Verzenios + ET	2,555	2,441	2,388	2,351	2,321	2,284	2,255	2,223	1,828	1,223	888	522	275	67	8	0
ET alone	2,565	2,449	2,404	2,363	2,327	2,273	2,235	2,186	1,785	1,194	871	527	281	64	10	0

CDK4 & 6=cyclin-dependent kinases 4 and 6; EBC=early breast cancer; ET=endocrine therapy; HR=hazard ratio; HER2-=human epidermal growth factor receptor 2-negative; HR+=hormone receptor-positive; IDFS=invasive disease-free survival.

REFERENCES:

1. Verzenio® (abemaciclib). Hong Kong Prescribing Information. Eli Lilly Asia, Inc. 2. Johnston SRD, Harbeck N, Hegg R, et al. J Clin Oncol. 2020 Dec 1;38(34):3987-3998. 3. Mayer EL, Dueck AC, Martin M, et al. Lancet Oncol. 2021 Feb;22(2):212-222. 4. Toi M et al. Poster presented at ESMO Breast Conference, Berlin, Germany 3-5th May 2022.

PP-AL-HK-0219 10/2022

everyday Verzenio® abemaciclib twice a day

Please scan the QR Code for complete Verzenio® Prescribing Information

Lilly

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