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Clinical Pharmacology

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1. PHESGO Hong Kong Product Information. **2.** Tan AR, *et al. Lancet Oncol* 2021;22:85–97. **3.** O'Shaughnessy J, et al. Eur J Cancer. 2021. Jul;152:223-232.

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Disclaimer

The Cover Shot

The cover shows a two-year-old American shorthair. In American homes, there are more cats than children! Cats have long been domesticated and were mummified in Ancient Egypt. Cats have superhuman abilities, such as seeing in the dark, hearing ultrasound and leaping roof-to-roof. They are quiet; they move around in silence and do not bark. The lifespan of cats has increased like humans. Thus, cats increasingly die of diseases of ageing such as cancer and kidney failure. Moreover, inbreeding has led to genetic disorders such as polycystic kidney disease and hypertrophic cardiomyopathy. Therefore, study of cats benefits both cats and humans.

Prof Bernard MY CHEUNG

First Vice-President
The Federation of Medical Societies of Hong Kong

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Editorial

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Editor

Prof Bernard MY CHEUNG

This issue of the Medical Diary is devoted to clinical pharmacology. It may seem like a specialist topic, but in fact, it is very wide and covers a large chunk of medicine, as the diverse articles in this issue illustrate. In the era of the COVID-19 pandemic, the importance of clinical pharmacology, and the discipline it represents, has never been so prominent. What is the treatment for COVID-19? How are new drugs found and how can they be evaluated for their efficacy and safety? How do you evaluate the efficacy and safety of vaccines? How do you judge whether an adverse event is related or unrelated to a drug or vaccine? These are the kind of questions to which clinical pharmacology provides the framework for addressing. On the part of the general public, never has the public discussed and debated so avidly efficacy and safety, adverse effects, the need for phase 3 clinical trials and so on. What seems dry and academic has become controversies on television, radio, internet and newspapers, and the stuff of everyday conversation.

In this issue, there is a discussion of what is or is not drug allergy by Dr Philip Li. Dr Patrick Leung writes on the latest recommendations on how to sedate the agitated patient. Prof Cyrus Kumana and Dr Harry Gill recall how the locally-discovered award-winning arsenic-based treatment for cancer was developed. Dr Joanne Chiu takes us through the complexities of new therapies for breast cancer, while Dr Elaine Chow takes us through the range of exciting new therapies for type 2 diabetes mellitus. Dr CL Cheung, a pharmacologist, reviews for us osteoporosis, a condition with increasing prevalence due to an ageing society lacking physical activity.

This issue of the Medical Diary is refreshingly different, because instead of focusing on an organ or disease, the spotlight is turned on drugs. Most of the undergraduate and postgraduate training in Medicine is about diagnosis, investigation and management. Even in postgraduate training, there is not much emphasis on the choice of drugs, and understanding their properties, including the harms as well as the benefits. As the Editor of this issue, I hope to kindle interest in this pervasive but inconspicuous speciality. I sincerely thank all the authors, who toiled tirelessly for this special issue, and the industrial partners for their unflinching support.

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*Among responders continuing on Aimovig, the percentage who cut their MMDs in half increased from 46% at 3 months, to 65% at 1 year and 69% at 5 years.[2-4]

CGRP, Calcitonin Gene-Related Peptide, MMDs, Monthly Migraine Days.

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ABBREVIATED PRESCRIBING INFORMATION **Aimovig Important note:** Before prescribing, consult full prescribing information. **Presentation:** Solution for injection, subcutaneous use: 1 mL prefilled pen contains 70 mg of erenumab. **Indications:** Aimovig is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month. **Dosage and administration: Adults:** The recommended dose of Aimovig is 70 mg administered subcutaneously every 4 weeks. Some patients may benefit from a dosage of 140 mg every 4 weeks. Aimovig is intended for patient self-administration in the abdomen, thigh, or, if someone else is giving the injection, also into the outer area of the upper arm. Administration should be performed by an individual who has been trained to administer the product. The needle cover of Aimovig pre-filled pen contains dry natural rubber, which may cause allergic reactions in individuals sensitive to latex. Consideration should be given to discontinuing treatment in patients who have shown no response after 3 months of treatment. Evaluation of the need to continue treatment is recommended regularly thereafter. The entire contents of the Aimovig pre-filled pen should be injected. **Special populations Pediatric patients:** The safety and effectiveness of Aimovig has not been studied in pediatric patients. **Geriatric patients:** No dose adjustment is necessary as the pharmacokinetics of erenumab are not affected by age. **Renal impairment/hepatic impairment:** No dose adjustment is necessary in patients with mild to moderate renal impairment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and precautions:** Patients with certain major cardiovascular diseases were excluded from clinical studies. No safety data are available in these patients. **Pregnancy, lactation, females and males of reproductive potential: Pregnancy:** Safety has not been established. As a precautionary measure, it is preferable to avoid the use of Aimovig during pregnancy. **Lactation:** It is not known whether erenumab is present in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breastfed infant cannot be excluded during this short period. Afterwards, use of Aimovig could be considered during breastfeeding only if clinically needed. **Females and males of reproductive potential:** Animal studies showed no impact on female and male fertility. **Adverse drug reactions: Common (≥1/100 to <1/10):** Injection site reactions, constipation, muscle spasm, pruritus. **Description of selected adverse reactions:** Injections site reactions include injection site pain, injection site erythema and injection site pruritus. A majority of injection site reactions were mild and transient. **Immunogenicity:** In pivotal studies the incidence of anti-erenumab antibody was 6.3% for the 70 mg dose (in-vitro neutralizing activity in 3 patients) and 2.6% for the 140 mg dose (no patients with in-vitro neutralizing activity). There was no impact of anti-erenumab antibody development on efficacy or safety of erenumab. **Interactions:** No effect on exposure of co-administered medicinal products is expected based on the metabolic pathways of monoclonal antibodies. No interaction with oral contraceptives (ethinyl estradiol/norgestimate) or sumatriptan was observed in studies with healthy volunteers. **Packs:** 1 mL prefilled pen contains 70 mg of erenumab. **Legal classification:** PTS1S3 Ref: EMA Aug 2018

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Oral Arsenic Trioxide Treatment for Acute Promyelocytic Leukaemia: A Novel Treatment Strategy Facilitated by Clinical Pharmacology

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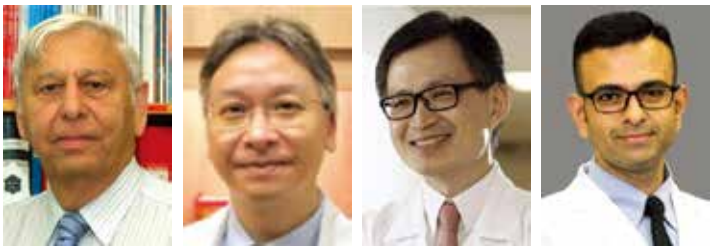

Prof Cyrus R KUMANA | Mr Raymond MAK | Prof Yok-lam KWONG | Dr Harinder GILL

Conflict of interest declarations

The University of Hong Kong holds the following patents on oral arsenic trioxide:

1. Oral arsenic trioxide for treatment of leukaemia (US patent 7,521,071 B2)
2. Oral arsenic trioxide for treatment of leukaemia (Japan patent 4786341)
3. Method for inhibiting cancer using arsenic trioxide (US patent 8,906,422 B2)
4. Formulation of oral compositions comprising arsenic trioxide (EP 1562616 B1)
5. Oral arsenic trioxide for treatment of rheumatoid arthritis (Japan patent P6049455)
6. Oral arsenic trioxide for treating inflammatory arthritis (US patent 10,092,595 B2)

CR Kumana, YL Kwong and H Gill are employees or associated with the University of Hong Kong. They have no other relevant conflicts of interest to declare.
R Mak has no relevant conflicts of interest to declare.

The tentacles of Clinical Pharmacology (the scientific study of drugs and their impact in clinical situations) spread far and wide. In that context, they impinge on issues that include: therapeutic efficacy and safety, pharmacology, toxicology, pharmacokinetics,† pharmacodynamics,‡ clinical trial methodology, drug treatment guidelines and appropriately targeted education, the manufacture of pharmaceuticals, cost-effectiveness considerations, and public health. Beyond these, they also involve government drug-regulatory authorities and hospital drug advisory committees, medication error surveillance and medico-legal disputes, the study of medication utilisation and prescribing (including drug treatment records), as well as a multitude of ethical conundrums. Notably, the Clinical Pharmacology story described in this article has ramifications in virtually all the aforementioned aspects of drug usage.

ARSENIC TRIOXIDE AS A THERAPEUTIC AGENT

Despite arsenicals having been around for several millennia, their role as genuinely effective haematological medicines has only been recognised during the last hundred and fifty years, and unsurprisingly the fascinating and checkered history of such developments has been the focus of several reviews.[1-3] Thus, whilst arsenic and its compounds are well documented as a means of poisoning, they were also purported to have numerous therapeutic properties. Arsenicals were probably introduced into Western Medicine around the eighteenth century. One such 'medicine' was Fowler's solution (also called Liquor Arsenicalis), which was a relatively crude, orally imbibed liquid formulation containing arsenic trioxide. In the late nineteenth century, reports from Germany and the US indicated that this orally taken medication was useful in the treatment of certain chronic leukaemias. Thereafter, it became a primary anti-leukaemic therapy used widely for this purpose for many decades, but its utility was always limited by its toxicities. Moreover, due to the advent of chemotherapy and radiotherapy after the Second World War, resorting to oral arsenic to treat leukaemias was gradually phased out. In the mid twentieth century though, new reports from Harbin in Mainland China described consistently promising haematologic responses in patients with acute promyelocytic leukaemia (APL) treated with intravenous arsenic trioxide (IV ATO). Reports from other nations soon followed and confirmed these observations. Such findings also appeared to be consistent with in-vitro studies describing ATO-induced apoptosis and differentiation of APL cells. Furthermore, around that time, molecular genetic advances showed that APL was almost always associated with a specific chromosomal translocation,* leading to the formation of an oncogenic fusion protein PML-RARA.[4] Notably, this molecular aberration identified patients responding more favourably to all-trans retinoic acid (ATRA) and ATO than to conventional regimens combining ATRA and chemotherapy. Later studies showed that arsenic is bound directly to the PML-RARA oncoprotein to enhance its degradation. Based on these discoveries

† Study of how the body handles/disposes of a given drug, over periods of time.
‡ Study of how a given drug impacts/influences the body (or tissues), over periods of time
* t(15;17)(q24;q21)

as well as on clinical trial findings, IV ATO treatment gained US Food and Drug Administration (FDA) approval and became recognised as an important therapeutic tool for the management of patients with APL.

Nevertheless, recourse to repeated 4 to 8 week courses of daily IV ATO infusions posed many challenges that seriously impeded patient quality of life. These challenges included: inconvenience (inevitably entailing hospitalisation and its attendant costs), cumbersome paraphernalia for intravenous infusion and maintaining vascular access, and prohibitive drug costs; currently, one month's typical treatment can retail at in excess of US$ 11,000.[5]

REJUVENATION OF ORAL ARSENIC TRIOXIDE

Based on what was known about the Hong Kong experience, local haematologists trolled through the meticulously written hospital case notes of local patients treated with Fowler's solution in the 1950s. The latter records consistently yielded objective clinical benefits as well as improved blood counts. These observations prompted a re-evaluation of a possible role for oral ATO to treat APL patients with a formulation prepared in accordance with Good Manufacturing Practice (GMP). Compared to IV dosing, oral treatment had the potential of conferring important quality of life benefits for patients, namely: greater convenience (enabling home treatment), avoidance of intravenous interventions, and huge savings in drug and other ancillary costs. Conceivably, therefore, such benefits might all be achieved with a degree of confidence and safety that was never attained with Fowler's solution.

These considerations prompted the development of a pure ATO solution for oral use, coupled with determination of its systemic bioavailability. The problems posed by this undertaking and how they were addressed/overcome (with the collaboration of hospital pharmacists) are outlined in Table 1. A comparison of arsenic bioavailability following IV and oral treatment is illustrated in Fig. 1 and its legend, and a summary of the main findings and their derivation is shown in Table 2 and its legend. A detailed account of this study and its findings was published in 2002, and showed that the systemic bioavailability estimates of arsenic attributable to either route of administration were essentially the same.[6]

SUBSEQUENT DEVELOPEMENTS

Having demonstrated that the oral ATO solution produced in Hong Kong (registered commercially as Arsenol®) and the commercially used IV formulation had comparable bioavailability, local haematologists began prescribing the newly produced oral formulation to APL patients. Furthermore, they used the same conventional daily dosages (typically 10 mg/day or 0.15mg/kg/day) as had been used parenterally. Compared with IV dosing, the new oral preparation was found to be at least as effective, safe, and well tolerated, and yet much more convenient and easier for patients to take; at the same time it was undoubtedly much more

Table 1. Production & Bioavailability Determination of an Oral As2O3 Formulation

Problem	How Addressed/Overcome
Securing Institutional Ethics Committee approval for the study protocol	The proposed unconventional bioavailability study protocol was approved based on the following compelling arguments: 1) All recruited patients would have a disease for which treatment with As_2O_3 would be indicated. 2) Each patient would need to give written informed consent. 3) Recruiting healthy volunteers to take arsenic would prove daunting and notable to reveal how the oral formulation was tolerated by sick diseased patients.
Sourcing pharmaceutical grade As_2O_3 (ATO) powder	Obtained from Sigma (USA).
The sparingly soluble suspension of As_2O_3 in water had to be completely dissolved to form a sterile solution	The suspension's pH was manipulated to 7.2 to yield a clear colourless solution containing 1 mg/ml of As_2O_3. Contrary to some recommendations, no fungicide was added as the entire preparation was conducted in a pharmaceutical isolator. Subsequent microbiology and chemical testing of samples yielded no fungi and an unchanged solute concentration exceeding one year (indicative of its minimum shelf-life).
Bioavailability testing in sick hospitalised patients precluded a conventional crossover design, blinding, or tolerability assessment.	In all, 9 patients were recruited using predefined inclusion/exclusion criteria and asked to refrain from seafood (an arsenic source) in the preceding week. Each patient received a 10mg IV infusion of As_2O_3 over 1 hour on day 1, followed by a 10mg oral dose 24 hours later. Just before initiating IV dosing and at predefined times over the next 48 hours, venous blood samples were drawn for determination of plasma and whole blood arsenic concentrations

Table 2. Area Under the Curve (AUC) of Plasma Arsenic Concentrations/Time Plots (Nanomolar-hours) (Adapted from table 2 in Kumana et al.[6])

	Day 1 (0-24 h) AUC attributed to IV Dose	Day 2 (24-48 h) AUC attributed to Oral Dose
Mean ± SEM	2673 ± 262	2640 ± 343
95% CI	1839-3507	1850-3430

For each of the 9 study patients, plasma arsenic concentration versus time plots from 0 to 48 hours (see fig. 1) were inscribed, and corresponding AUCs were derived using standard computer software (GraphPad Prism Version 3) incorporating the trapezoidal rule. The 0 to 24 h AUCs were regarded as attributable to IV dosing on day 1. The difference between the gross 24 to 48 h AUC and that extrapolated for the day 2 decay in levels ensuing after IV dosing on day 1, was regarded as the AUC attributable to oral dosing between 24 and 48 hours. Respective AUCs for each patient (post IV dosing on day 1 and attributable to oral dosing on day 2) were taken to be measures of immediate arsenic bioavailability attributable to each formulation.

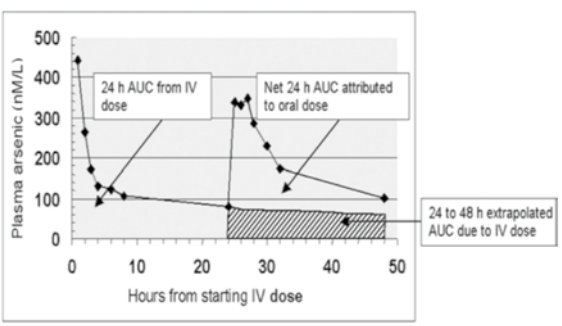

Fig. 1. Area Under the Curve (AUC) of arsenic levels attributed to intravenous and oral dosing of arsenic trioxide in a single patient (nanomolar-hours). [Adapted from Kumana et al[6] with permission]

cost and time effective to deliver.[3] Others also reported similar findings with subsequently developed (though differently prepared) oral formulations.[7,8] Interestingly, ATO given IV has been repeatedly linked to the occurrence of dangerous cardiac arrhythmias (Torsades de Pointes) and sudden death, and it seems that this risk is largely mitigated[#] when using the oral route.[9] This added advantage of oral dosing, formed the basis for securing a US patent for the treatment of APL patients with the Hong Kong produced oral As_2O_3 formulation, and soon after, similar patents were also granted from other parts of the world.[3]

In the ensuing years, numerous phase II trials have been conducted using oral ATO treatment with and without other active agents (including ATRA, ascorbic acid, and a plethora of various chemotherapeutic agents), some of which may act synergistically with arsenic. The latter investigations confirmed the long-term efficacy and safety of oral ATO used instead of IV dosing to be a suitable treatment strategy for maintaining patients in remission and improving disease free survival as well as overall survival.[3] Compared with IV dosing moreover, these benefits were achieved with much less quality of life disruption and at a much lower cost.[3-6] More recent studies in newly diagnosed or relapsed APL patients have shown that when oral ATO is incorporated into induction and re-induction regimens, excellent long-term outcomes and cure can be achieved.[10-12]

In Hong Kong, Arsenol® packaged as shown in Fig. 2, together with an updated package insert in English and Chinese - is being produced by a local manufacturer (Jacobson Pharma Corporation Ltd). Moreover, the Hong Kong Department of Health and the Hong Kong Hospital Authority have approved Arsenol's registration, with a caveat that its use was to be part of an agreed territory-wide service, coordinated by a single tertiary hospital haematology centre. Furthermore, there could also be a role for ATO treatment for patients with other haematological and non-haematological disorders, including: nucleophosmin 1 (NPM1)-mutated acute myeloid leukaemia (AML), lymphoma, and lung cancer, as well as certain autoimmune disorders.[13-20] If these possibilities are borne out, the same advantages are likely to ensue for oral as opposed to IV dosing as apply to APL.

Fig 2. The modern Good Manufacturing Practice (GMP)-grade oral arsenic trioxide (Arsenol ®) (Courtesy of Jacobson Pharma Corporation)

CONCLUSION

This article describes the production of a high quality oral ATO formulation (Arsenol®) facilitated by Clinical Pharmacology input, which has been approved to treat patients by the Hong Kong Department of Health and the Hong Kong Hospital Authority. Consequently, local APL patients treated with this oral preparation can enjoy the same therapeutic efficacy as those receiving IV doses, but with the added benefits of far more convenience (enabling home treatment), greater affordability, and lower risks of cardiotoxicity. For individual patients and societies at large, the latter advantages can be regarded as important and genuinely life-changing and cost-saving. Moreover, it is anticipated that in the not-too-distant future - this highly effective, inexpensive, and convenient form of treatment will become more widely available commercially around the world. Ironically, stemming from the therapeutic developments described here, APL that was once regarded as among the most malignant and costly to treat leukaemias - has now become among the most curable[21] and affordable to confront conveniently with oral therapy.

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[#] Possibly because arsenic's gradual entry into the circulation after oral dosing seldom gives rise to excessive peak plasma levels, whereas the much higher peak concentrations attained after IV infusions risk toxicity.

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Current Treatment for Metastatic Breast Cancer

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INTRODUCTION

Breast cancer is the most common female cancer in Hong Kong, affecting 1 in 14 women in their lifetime[1]. Although the majority of breast cancer is diagnosed at an early stage when curative resection is feasible, the cancer recurs in many patients and causes death. The prognosis and outcome of patients with metastatic breast cancer rely on effective drug therapy that can both prolong survival and improve the quality of life.

Drug treatment for metastatic cancer is determined by the phenotypes. Based on the overexpression of hormone-receptors and epidermal growth factor receptor type 2 (HER2), breast cancer can be divided into HER2-positive, hormone receptor (HR)-positive, or triple negative breast cancer (Fig. 1).

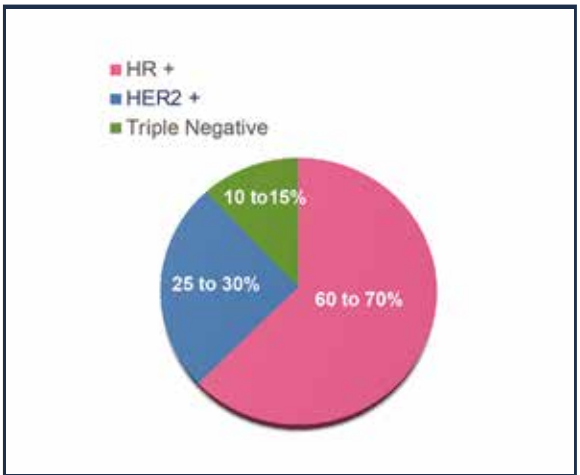

Fig 1. Subtypes of breast cancer
Abbreviation: HR – hormone receptor; HER2 – human epidermal growth factor receptor 2

HER2-POSITIVE BREAST CANCER

HER2-positive breast cancer is an aggressive subtype, constituting about 1/3 of all breast cancer. Since the development of the first anti-HER2 targeted therapy two decades ago, there has been tremendous progress in drug development for this disease. Fig. 2 summarises the development of anti-HER2 treatment by their year of approval by the U.S. Food and Drug Administration (FDA). The first anti-HER2 therapy is trastuzumab, a large-molecule antibody, which works by binding to the HER2 receptor on the surface of breast cancer cells and blocking the downstream growth signalling. Trastuzumab can also activate antibody-dependent cellular cytotoxicity (ADCC); thus it interplays with the immune system in fighting cancer. Many subsequent anti-HER2 treatments are built on trastuzumab. For instance, pertuzumab blocks hetero-dimerisation of HER2 and HER3 surface receptors and facilitates the efficacy of trastuzumab. Addition of pertuzumab to trastuzumab-based treatment prolonged the progression-free survival by 6 months, and reduced death by 34%[2]. Trastuzumab emtasine (T-DM1), the first antibody-drug conjugate (ADC) that links trastuzumab to chemotherapy, works like targeted chemotherapy and offers the advantage of both drugs without the typical toxicities of chemotherapy. It also significantly reduced progression and death, as compared with the standard of care[3]. The second ADC, trastuzumab deruxtecan (TDxD) is now available. It has a stronger chemotherapy partner and could shrink HER2-positive breast cancer in half of the patients who have progressed on existing standard-of-care anti-HER2 therapy[4]. The effect on overall survival is not known yet. Anti-HER2 therapy also comes in oral form. These are small-molecule tyrosine kinase inhibitors that can bind to an intracellular area of tumour cells. Due to their small size, they have appreciable activity for patients with brain metastasis[5,6]. As the patent for

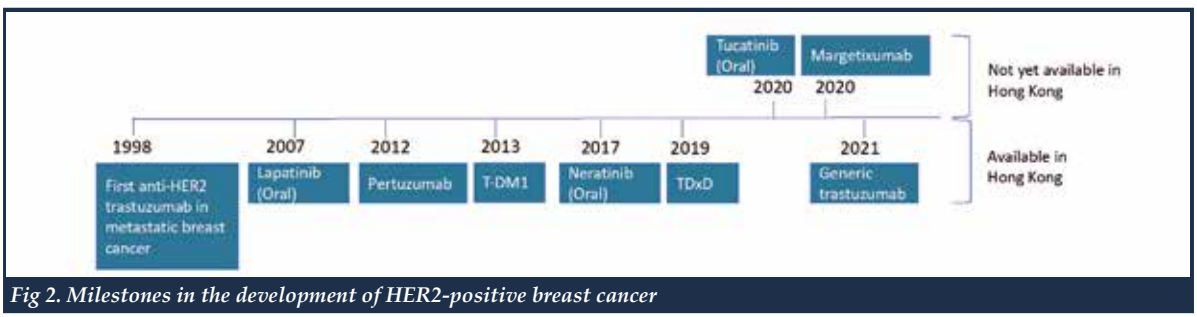

Fig 2. Milestones in the development of HER2-positive breast cancer

the branded trastuzumab has expired, we have seen a number of generic formulations of this drug in the market recently. The treatment of HER2-positive breast cancer is becoming more affordable.

HORMONE RECEPTOR-POSITIVE BREAST CANCER

Around 60-70% of breast cancer belongs to hormone receptor (HR)-positive subtype. This subtype tends to be more slowly growing and many patients can survive for many years. In the absence of excessive tumour burden threatening organ function, hormonal therapy would be the standard of care until the disease becomes resistant to available hormonal therapy. Most patients would receive hormonal therapy, be it selective estrogen-receptor response modulators (e.g. tamoxifen), aromatase inhibitor (AI), or estrogen receptor degrader, as a single agent or in the combination with cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors. There are now 3 CDK4/6 inhibitors on the market – palbociclib, ribociclib, and abemaciclib. CDK4/6 inhibitors have revolutionised the treatment of HR-positive breast cancer. Not only can they prolong the use of hormonal therapy and decrease the chance of progression by close to 50%, but some of them have also already been proven to prolong the overall survival in these patients[7,8]. Upon disease progression while on these agents, clinicians will resort to molecular testing of the tumour, and to explore if the patients would be candidates for targeted agents such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) antagonist (e.g. alpelisib)[9], or Poly(ADP-ribose) polymerase-1 (PARP) inhibitor (e.g. olaparib, talazoparib)[10,11]. For patients who have exhausted all treatment using hormonal therapy or targeted agents, or for those patient who have heavy tumour burden with visceral crisis, chemotherapy would be used to stabilise the disease. Fig. 3 summarises the algorithm for the treatment of metastatic HR-positive breast cancer.

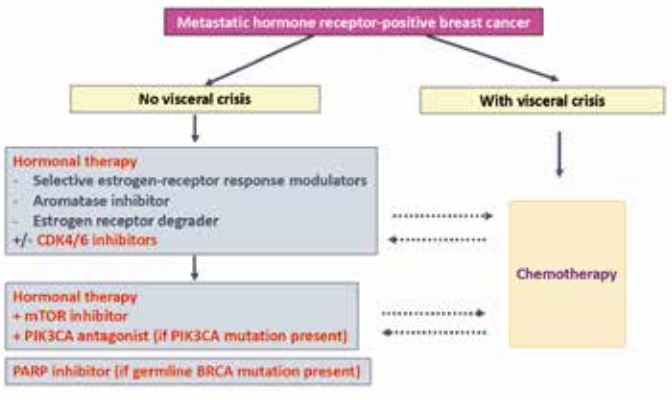

Fig 3. Algorithm in the treatment of hormone receptor-positive metastatic breast cancer
Abbreviation: BRCA – Breast cancer gene; CDK4/6 – cyclin-dependent kinases 4 and 6; mTOR – mammalian target rapamycin; PIK3CA – phosphatidylinositol-4,5-bisphosphate 3- kinase; PARP – poly adenosine diphosphate-ribose polymerase

TRIPLE NEGATIVE BREAST CANCER

Triple negative breast cancer (TNBC) is an aggressive breast cancer. It carries a poorer prognosis than the other two forms of breast cancer. The average overall survival is 12 to 18 months only. Molecularly it is heterogeneous yet most are 'basal-like' and of higher grade. Chemotherapy is the mainstay treatment traditionally. Patients rotate from one chemotherapy regimen to another one until complete resistance. The advance of immunotherapy with checkpoint inhibitor, such as atezolizumab or pembrolizumab, showed preliminary effect in the treatment of TNBC before[12,13]. However, due to inconsistency in longer-term outcome results, the indication of atezolizumab in TNBC was withdrawn by the company recently. Pembrolizumab remained an approved option for locally advanced TNBC at the moment with significant improvement in the pathological complete response[14]. When patients present with TNBC at young age, with the bilateral or contralateral disease, or known family history of breast cancer, the presence of germline mutation in breast cancer gene 1 (BRCA 1) or BRCA 2 mutation must be considered. Patients who carry this mutation can receive poly adenosine diphosphate-ribose polymerase (PARP) inhibitor as part of their treatment[10,11] and currently it is the only oral targeted therapy available for TNBC. Most recently, antibody-drug conjugate (ADC) also plays a role in the treatment of TNBC. Sacituzumab govitecan is a monoclonal antibody against trophoblast cell-surface antigen (TROP)-2 coupled with a chemotherapeutic agent. It has been granted accelerated approval by the U.S. FDA for patients with metastatic TNBC who have received at least 2 prior therapies. Patient on this drug achieved median overall survival of 12.1 months compared with 6.7 months of the control arm[15].

SUMMARY

Treatment of metastatic breast cancer depends on the phenotype. Although chemotherapy can be used in all subtypes, the use of targeted therapy is becoming increasingly important, and genetic testing should be considered when appropriate. The use of antibody-drug conjugate in both HER2-positive and TNBC is anticipated in the near future.

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Radiology Quiz

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MBBS, FRCR

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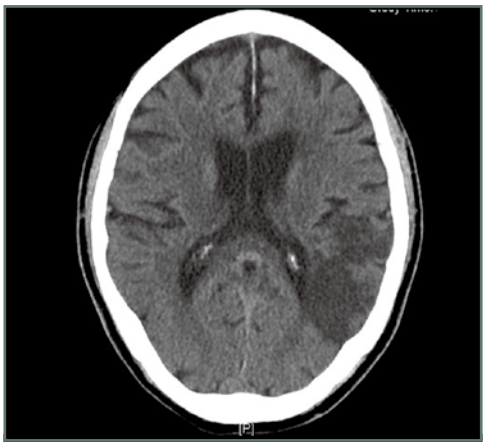

Case 2

Questions

1. What is the diagnosis?
2. What is the next step of investigation?
3. What are the possible complications?
4. What are the CT radiological signs of MCA cerebral infarct?

(See P.36 for answers)

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Cardiac:

- HFpEF[2]
- HF therapy intolerance*[3]
  *The standard therapies for HF, including ACEI, ARB, and BB[3]
- LVH on Echo[2]
- Imaging and ECG discrepancy**[2]
  **Imaging finding of LVH and normal/low QRS voltage on ECG[2]

Non-cardiac:

- Orthopaedic syndromes (e.g carpal tunnel syndrome, lumbar spinal stenosis and bicep tendon rupture)[2]
- Polyneuropathy[2]
- Family history of TTR amyloidosis[4]

Abbreviations: ACEI: Angiotensin-converting enzyme inhibitors; **ARB:** Angiotensin-receptor blockers; **ATTR-CM:** Transthyretin amyloid cardiomyopathy; **BB:** Beta blockers; **ECG:** Electrocardiogram; **Echo:** Echocardiography; **HF:** Heart failure; **HFpEF:** Heart failure with preserved ejection fraction; **LVH:** Left ventricular hypertrophy; **TTR:** Transthyretin
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Primary Prevention of Osteoporosis in Hong Kong: A Brief Update

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 October 2021.

INTRODUCTION

Osteoporosis is a prevalent disease especially among the elderly. Compared to other chronic diseases of the aged, osteoporosis receives little attention not only among the general public, but also among healthcare professionals. Unlike many other diseases, osteoporosis could be totally asymptomatic, and is therefore commonly described as a silent disease. Patients may only realise the presence of osteoporosis when they sustain a fracture. Among all osteoporotic fractures, hip fracture is known to be associated with the highest risk of morbidity, immobility, and mortality. According to our recent projection in Asia,[1] if the incidence of hip fracture remains unchanged, there will be more than 25,000 hip fractures happening every year in Hong Kong by 2050, which will lead to an annual direct medical cost of more than 1.8 billion Hong Kong dollars.[1] Knowing that Hong Kong holds the highest life expectancy in the world, it is an urgency to prepare for the "fracture tsunami" in Hong Kong.

OSTEOPOROSIS SCREENING

To reduce fracture-associated burden, primary prevention is of public health importance. In 2019, several non-governmental organisations, including Osteoporosis Society Hong Kong (OSHK), Society of Hospital Pharmacists of Hong Kong, Health in Action, Osteoporosis Concern Group, Silveriders, and Department of Pharmacology and Pharmacy, the University of Hong Kong, formed "The Osteoporosis Primary Care Task Force". The Task Force aims to promote universal Dual-energy X-ray absorptimetry (DXA) screening to reduce the burden of osteoporotic fracture. Since universal DXA screening may not be cost-effective, our research team recently developed a simple 3-question questionnaire called Chinese Osteoporosis Screening Algorithm (COSA) to predict risk of osteoporosis, incorporation of COSA in osteoporosis screening may improve cost-effectiveness. COSA was developed using the data from the Hong Kong Osteoporosis Study,[2] the first ever osteoporosis cohort study of all ages in Asia, and the data should have a high generalisability to the Hong Kong population. Based on our on-going validation study, the positive predictive value was approximately 0.5, meaning that ~50% of the "high risk patients" suggested by the COSA questionnaire are osteoporotic. This simple screening tool is expected to largely reduce the number of people requiring DXA scans, and to facilitate the implementation of population-wide screening. The pilot testing of COSA and its related management protocol has been implemented in Kwai Tsing District Health Centre (DHC). The incorporation of this protocol in future DHCs may play an important role in primary prevention of osteoporosis. In Hong Kong, since the mean age of hip fracture is approximately 82.1 years,[3] reaching out to the "oldest old" (defined as people aged 80 or above) is important. Recently, a risk score (Hong Kong Osteoporosis Study [HKOS] score) has also been developed to predict fracture risk in the oldest old.[4] In the validation study, the risk score achieved an AUC of 0.81 in predicting hip fracture.[4] This risk score seemed to have out-performed other risk scores, like FRAX and QFracture. Given that the HKOS risk score targets the most vulnerable population with the highest risk of hip fracture, the application of this risk score in predicting hip fracture may be clinically relevant in reducing hip fracture in Hong Kong.

PHARMACOLOGICAL INTERVENTION

Management of osteoporosis can be broadly categorised into pharmacological (Table 1) and non-pharmacological interventions (Table 2)[5]. In terms of pharmacological intervention, alendronate is the first-line medication commonly used to treat osteoporosis in Hong Kong. Our recent studies showed that alendronate and other nitrogen-containing bisphosphonates could potentially reduce the risk of incident cardiovascular diseases[6] and pneumonia.[7] These observations are in line with a subsequent large-scale randomised controlled trial.[8-10] Nevertheless, poor treatment adherence of alendronate reduces the significance of the drug in fracture prevention. Newer non-oral medications, e.g., zoledronate and denosumab that only require intravenous infusion once a year or subcutaneous injection twice a year, may enhance treatment adherence and lead to a better treatment outcome.

For those with severe osteoporosis, promotion of bone formation is required to build stronger bone effectively, instead of purely depending on inhibition of bone resorption. Thus, anabolic agents are recommended for patients with severe osteoporosis at high risk of fracture. Currently, there are two anabolic agents available in

Hong Kong. The first anabolic agent available in the market is teriparatide, which is a recombinant human parathyroid hormone (PTH) 1-34. Daily subcutaneous injection of teriparatide leads to the anabolic window of PTH-signaling, which allows the net gain of bone formation. However, while teriparatide has a significant effect in improving Bone Mineral Density (BMD) at the lumbar spine, its effect on hip BMD, and hence hip fracture prevention, is controversial. On the other hand, romosozumab has recently been introduced into the market in Hong Kong. Romosozumab is a monoclonal antibody that inhibits the protein sclerostin, which is an antagonist of the anabolic Wnt/β-catenin signalling pathway. Indeed, romosozumab confers dual action, promoting bone formation and inhibiting bone resorption at the same time, leading a wider anabolic window than teriparatide. A head-to-head comparison trial showed that monthly subcutaneous injection of romosozumab led to a significantly higher bone mass gain at both spine and hip than teriparatide.[11] Notably, in view of the need for balancing the risks and benefits, teriparatide and romosozumab can only be used for two years and one year respectively. After that, transition to anti-resorptive agents is recommended to extend the beneficial effect of anabolic agents on bone.

In 2013, the OSHK published a clinical guideline of osteoporosis treatment,[12] which was the first risk-based treatment recommendation in the world. Now that the new anabolic agent romosozumab is available in the market, OSHK will likely update the clinical guideline. In the presence of different choices of anti-osteoporosis agents for different needs, pharmacological intervention remains the most effective strategy in improving bone mass and reducing fracture risk.

Table 1. Anti-osteoporosis agents available in Hong Kong (modified from the literature [12])

Anti-resorptive agents
Bisphosphonates (e.g., alendronate, ibandronate, risedronate, zoledronate)
Denosumab
Calcitonin
Hormone replacement therapy
Raloxifene
Anabolic agents
Teriparatide
Romosozumab
Uncoupling agent
Strontium ranelate*

*Due to potential increased risk in adverse cardiac events, it is rarely in use now.

Table 2. Common non-pharmacological interventions for osteoporosis management (summarised from the literature [5])

Adequate protein intake
Avoidance of excessive caffeine intake
Education and psychosocial support
Fall prevention
Maintaining sufficient circulating vitamin D levels
Muscle strengthening
Reduction of alcohol consumption
Smoking cessation
Sufficient calcium intake (either via diet or supplementation)
Weight-bearing exercise

UPDATES ON NON-PHARMACOLOGICAL INTERVENTION: VITAMIN D, FALL PREVENTION, AND CAFFEINE INTAKE

Table 2 summarises non-pharmacological interventions for osteoporosis according to a systematic review of clinical practice guidelines.[5] Most of these interventions are well known to healthcare professionals and the general public, but there are several points to note regarding calcium and vitamin D, fall prevention, and caffeine intake. Sufficient calcium intake and vitamin D levels, either through diet or sunlight exposure, are important in maintaining bone health. However, intake of calcium-rich and vitamin D-rich foods, including dairy products, are generally low in the Chinese population. Adding to the fact that many people do not have sufficient sunlight exposure, possibly due to lack of outdoor activity and/or use of sunscreen products, there is a high prevalence of vitamin D deficiency and insufficiency in the Hong Kong population.[13] Thus, calcium and vitamin D supplements are commonly used to compensate for the deficiency. For people aged 70 or above, the Institute of Medicine recommends 800 IU of dietary allowance and 4,000 IU of tolerable upper intake levels of vitamin D. It is not uncommon that high-dose vitamin D is prescribed to correct its deficiency. However, a recent trial showed that high-dose vitamin D (4,000 IU and 10,000 IU per day) reduced bone mass and quality,[14] probably through alteration of calcium metabolism,[15] as opposed to the general belief that higher doses of vitamin D could lead to better bone health. Another trial showed that high-dose vitamin D (60,000 IU per month) increased the risk of falls.[16] Prescription of high-dose vitamin D could be potentially unsafe, and may result in worsened bone health and higher risk of fall.

In terms of risk of fall, although fall prevention clinics or services are available in Hong Kong, incidence of falls has never abated. Our recent study evaluated the territory-wide secular trend of hospitalised falls from 2005 to 2018 and found that the incidence of falls among people aged 60 or above has been increasing from 11.55 per 1000 person-years in 2005 to 15.24 per 1,000 person-years in 2018,[17] resulting in an average annual percentage change of +2.3% (95% CI: +1.8% to +2.8%). Similarly, the incidence of fall-related severe injuries has also been increasing.[17] Since fall-related injuries include fracture and other severe consequences such as intracranial bleeding and spinal cord injury, an effective and strategic fall prevention programme should be developed and implemented in our community to avert fall-related fracture and other related injuries.

Caffeine intake has long been known to increase calcium excretion, thus potentially increasing calcium loss and negative calcium balance. Coffee is one of the most consumed caffeine-rich beverages. Although it was reported that coffee intake was inversely associated with BMD,[18,19] these studies were reported in non-Asian population. Our recent study[20] using data from more than 7,000 participants from the HKOS showed that habitual coffee intake was indeed positively associated

with lower BMD at both spine and hip. The similar positive association between coffee intake and BMD loss was also reported in Korea.[21] Thus, excessive caffeine intake should be avoided; but habitual coffee intake, in appropriate amounts, may lead to better bone health.

CONCLUSION

In conclusion, osteoporosis and its associated fracture remain a huge public health issue in Hong Kong, and primary prevention plays a key role in fracture prevention. Using new tools to screen people at high risk of osteoporosis and fracture may allow earlier case identification and appropriate and timely pharmacological and non-pharmacological interventions, which in turn may subsequently reduce the burden of osteoporosis.

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PFS

84%

risk reduction of progression or death vs. placebo[4]

(HR=0.16; 95% CI: 0.1–0.27)

PFS & OS results after 9 months of additional follow-up is consistent with primary analysis[3,4]

OS

58%

risk reduction of death vs. placebo[4]

(HR=0.42; 95% CI: 0.26–0.67)

Qinlock can inhibit a broad spectrum of KIT/PDGFRa mutations[5]

Study design: INVICTUS was a global, multicenter, randomized, double-blind, placebo-controlled Phase 3 trial in 129 patients who had received ≥3 prior anticancer therapies for advanced GIST. The primary endpoint was PFS based on BICR using modified RECIST 1.1 criteria. Secondary endpoints were ORR by BICR, OS, and safety. Participants were randomized 2:1 to receive 150mg QD QINLOCK (n=85) or placebo (n=44). Treatment continued until disease progression or unacceptable toxicity. At disease progression, placebo patients could crossover to QINLOCK. After the primary analysis data cutoff date (May 31, 2019), 9 months of additional follow-up was conducted.[3,4]
Abbreviations: BICR, blinded independent central review; GIST, gastrointestinal stromal tumor; KIT, proto-oncogene encoding receptor tyrosine kinase protein; NCCN®, National Comprehensive Cancer Network®; ORR, objective response rate; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors; PDGFRα, platelet-derived growth factor receptor α; PFS, progression-free survival; QD, once a day; TKI, tyrosine kinase inhibitor.

References: 1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs) V.1.2021 ©National Comprehensive Cancer Network, Inc. 2020. Accessed June 28, 2021. **2.** QINLOCK (Ripretinib) [Prescribing Information]. Hong Kong; Version: Nov 2020. **3.** Blay JY et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020;21(7):923-934. **4.** Gelderblom H et al. Clinical benefit with ripretinib as fourth-line treatment in patients with advanced gastrointestinal stromal tumor: Update from the phase 3 INVICTUS study. Poster presented virtually at: 2020 Connective Tissue Oncology Society (CTOS) Virtual Meeting; November 18-21, 2020. Poster 145. **5.** Schöffski P, Bauer S, Heinrich M, et al. Ripretinib demonstrated activity across all KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Analysis from the phase 3 INVICTUS study. Poster presentation at: 2020 Connective Tissue Oncology Society Virtual Meeting; November 18-21, 2020.

QINLOCK (Ripretinib) TABLETS 50MG – ABBREVIATED PRESCRIBING INFORMATION

INDICATIONS Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. **DOSAGE AND ADMINISTRATION** 150mg (three 50mg tablets) taken orally once daily. Dosage reduction for adverse reaction is 100mg orally once daily. Permanently discontinue QINLOCK in patients who are unable to tolerate 100 mg orally once daily. Please refer to the full prescribing information for recommended dosage modifications for adverse reactions and missed dose. Qinlock is not indicated in pediatrics (<18 years old). No dose adjustment is required for geriatrics (≥65 years old). Renal impairment - No dose adjustment is recommended for patients with mild and moderate renal impairment (creatinine clearance (CrCl) 30 to 89 mL/min estimated by Cockcroft-Gault). The pharmacokinetics and safety of Qinlock in patients with end-stage renal disease (CrCl <15mL/min estimated by Cockcroft-Gault or requiring dialysis) or severe renal impairment (CrCl 15 to 29 mL/min) have not been studied. Hepatic impairment - No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin 1.0 to 1.5 x ULN). The pharmacokinetics and safety of Qinlock in patients with moderate or severe hepatic impairment have not been studied. **CONTRAINDICATIONS** Hypersensitivity to ripretinib or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. **WARNINGS AND PRECAUTIONS** The following are clinically significant adverse events: 1) Cardiac dysfunction. Cardiac failure and Grade 3 decreased ejection fraction has occurred in clinical study. Cardiac dysfunction has led to dose discontinuation. An assessment of the ejection fraction by echocardiogram or MUGA scan is recommended prior to initiation and during treatment, as clinically indicated. Permanently discontinue Qinlock for Grade 3 or 4 left ventricular systolic dysfunction; 2) Hypertension. Higher incidence of hypertension in patients treated with Qinlock than in placebo-treated patients in clinical study. Do not initiate Qinlock in patients with uncontrolled hypertension. Adequately control blood pressure prior to initiating Qinlock; 3) New primary cutaneous malignancies. Squamous cell carcinoma (SCC) of the skin and melanoma, actinic keratosis, keratoacanthoma and melanoma were reported in patients who received Qinlock in clinical study. Dermatological assessment should be performed when initiating Qinlock and patients should receive dermatological examinations routinely. Other warnings and precautions include cardiac ischaemic events, hypersensitivity, wound healing, reproduction, fertility, palmar-plantar erythrodysesthesia syndrome (PPES) and photosensitivity. **PREGNANCY AND BREAST-FEEDING** Pregnancy - Qinlock should not be administered to pregnant women. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception to commence 2 weeks prior to treatment, during treatment and for at least one complete uterine cycle after the final dose of Qinlock. Breast-feeding - Advise women not to breastfeed during treatment and for at least 2 weeks after the final dose. **ADVERSE REACTIONS** The most common adverse events (≥20%) observed in clinical study were alopecia, fatigue, nausea, abdominal pain, constipation, myalgia, diarrhea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, and vomiting. Serious adverse events occurred in 31% of patients who received Qinlock. Serious adverse reactions that occurred in >2% of patients were abdominal pain (4.7%), anemia (3.5%), nausea (2.4%), vomiting (2.4%). Dosage interruptions due to an adverse event occurred in 23.5% of patients who received Qinlock. Adverse events requiring dosage interruption in >2% of patients included nausea (3.5%), increased blood bilirubin (2.4%), and PPES (2.4%). Dose reductions due to an adverse event occurred in 7.1% of patients who received Qinlock. Adverse events resulting in a dose reduction in >1.2% of patients were abdominal pain, agitation, alopecia, arthritis, dermatosis, gastrointestinal disorder, hyperesthesia, myalgia, PPES, and decreased weight. Permanent discontinuation due to an adverse event occurred in 8.2% of patients who received Qinlock. Adverse events resulting in permanent discontinuation in >1% of patients included general physical health deterioration (2.4%), anemia (1.2%), cardiac failure (1.2%), PPES (1.2%), and vomiting (1.2%). **DRUG INTERACTIONS** In vitro data suggested that CYP3A4/5 is the major metabolizer of ripretinib. Potential interactions may occur with drugs/foods/herbs that are inhibitors or inducers of this enzyme system. Monitor patients more frequently for adverse reactions if Qinlock is given concurrently with a strong CYP3A inhibitor. Avoid concomitant use of Qinlock with strong CYP3A inducers. Monitor patients who ingest grapefruit juiced while taking Qinlock. Avoid concomitant use with St. John's wort. Please refer to the full prescribing information before prescribing. Ref. HKPI Nov 2020 (Canadian PM 19 Jun 2020)

zai Lab

Zai Lab (Hong Kong) Limited
Room 2301, 23/F, Island Place Tower, 510 King's Road, North Point, Hong Kong
Tel : +852 3844 8100 Fax : +852 3844 8188
HK-QIN-202107-01

QINLOCK® (ripretinib) 50 mg tablets

MCHK CME Programme Self-assessment Questions

Please read the article entitled "Primary Prevention of Osteoporosis in Hong Kong: A Brief Update" by Dr Ching-lung CHEUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 October 2021. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

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

1. **Osteoporosis can be asymptomatic.**
2. **Fracture prediction tools are available.**
3. **Adherence to oral alendronate is well-documented to be poor.**
4. **Denosumab is an anabolic agent.**
5. **Romozosumab can increase bone formation and reduce bone resorption at the same time.**
6. **Romozosumab's beneficial effect disappears quickly upon stopping treatment.**
7. **There is a clinical management guideline on osteoporosis specific for Hong Kong.**
8. **High-dose vitamin D (>4000 IU/day) is good for bone health.**
9. **Incidence of hospitalised falls has been decreasing in Hong Kong.**
10. **Habitual coffee intake, even not in excess, is detrimental to bone health.**

ANSWER SHEET FOR OCTOBER 2021

Please return the completed answer sheet to the Federation Secretariat on or before 31 October 2021 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Primary Prevention of Osteoporosis in Hong Kong: A Brief Update

Dr Ching-lung CHEUNG

Associate Professor
Department of Pharmacology and Pharmacy, the University of Hong Kong, Pokfulam, Hong Kong

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

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

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

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

Answers to September 2021 Issue

Diabetes Mellitus - Who to Screen and What to Monitor for Renal Complications

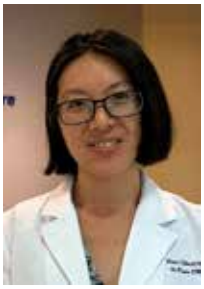
1. T 2. F 3. F 4. T 5. T 6. F 7. T 8. T 9. T 10. T

Sodium Glucose Co-transporter 2 Inhibitors: Glucose Lowering and Beyond

Dr Elaine CHOW

MBChB, PhD, MRCP(UK), FHKAM

Clinical Assistant Professor, Department of Medicine and Therapeutics
Division of Clinical Pharmacology, The Chinese University of Hong Kong



Dr Elaine CHOW

INTRODUCTION

Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have been regarded as a game changer in the landscape of newer glucose-lowering drugs (GLDs), demonstrating significant improvements in hard cardiovascular (CV) endpoints where other GLDs have been neutral. A series of landmark cardiovascular outcome trials have shown SGLT2 inhibitors are associated with consistent reductions in CV death and heart failure hospitalisation, progression of chronic kidney disease (CKD) in patients with type 2 diabetes (T2D). The cardiorenal benefits of SGLT2 inhibitors extend beyond the diabetic population, showing a similar reduction in heart failure and CKD in non-diabetic individuals. SGLT2 inhibitors promote weight loss, lowers blood pressure with low hypoglycaemic potential but are associated with risks of genitourinary infection and euglycaemic diabetic ketoacidosis (DKA). In this review, we shall summarise the latest evidence for the use of SGLT2 inhibitors in diabetic and non-diabetic populations for cardio-renoprotection and beyond.

ACTIONS OF SGLT2 INHIBITORS

SGLT2 inhibitors, also known as the gliflozins, primarily act on the SGLT2 in the proximal tube of the kidney where 97% of filtered glucose is reabsorbed under normoglycaemic conditions. SGLT2 inhibition promotes glycosuria and excretion of glucose load. When compared with placebo, SGLT2 inhibitors are associated with a reduction in HbA1c by 0.6-0.9% regardless of background therapy.[1] The degree of reduction in plasma glucose is proportionate to the ambient glucose concentrations and the rate of glomerular filtration. One of the advantages of SGLT2 inhibition is that its glucose-lowering actions occur independently of insulin and is thus associated with a low risk of hypoglycemia. Due to its glycosuric effects, SGLT2 inhibitors can promote negative energy balance and weight loss. Most studies report 2-3 kg weight loss in the initial six months of treatment which then stabilises.[1] SGLT2 inhibitors also reduce plasma volume. The use of SGLT2 inhibitors are generally associated with a decrease in systolic and diastolic blood pressure by 4-6 mmHg and 1-2 mmHg, respectively (Fig. 1).

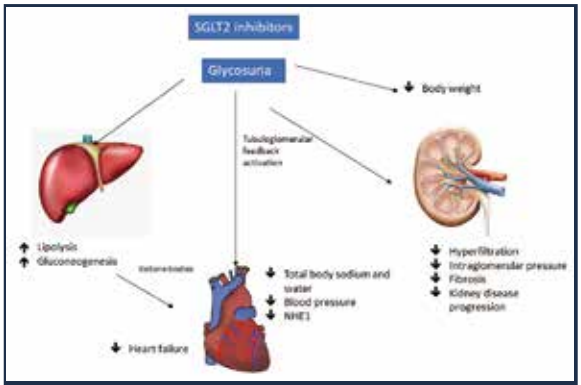


Fig. 1 Actions of sodium glucose cotransporter 2 inhibitors
SGLT2 inhibitors have pleiotropic effects. Glycosuric actions will reduce body weight. SGLT2 inhibitors activate tubuloglomerular feedback and have been shown to reduce hyperfiltration and intraglomerular pressure in the kidneys. These mechanisms may prevent kidney disease progression. It also reduces the total body sodium and water, reducing blood pressure, inhibiting sodium-hydrogen exchanger (NHE1) in the heart and kidneys.
Additionally, SGLT2 inhibitors can increase lipolysis, favour ketone body formation which can improve substrate utilisation in the heart. Adapted from[20]

SGLT2 INHIBITORS AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

Although originally developed as a glucose-lowering agent, rather unexpectedly, SGLT2 inhibitors significantly improve cardiovascular-renal outcomes in type 2 diabetes in randomised controlled studies. In the Empagliflozin, Cardiovascular Outcome Event trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME 2 empagliflozin was associated with a significantly lower risk of major adverse cardiac events (MACE) (hazard ratio HR 0.6 [95% CI 0.74-0.99, p =0.04]) as compared with placebo in diabetes patients with established CVD.[2-3] This was mainly driven by a 38% reduction in CV death. Hospitalisation for heart failure was also reduced by 35%. The Canagliflozin Cardiovascular Assessment Study (CANVAS) study, which recruited type 2 diabetes patients at high CV risk, including those without established CVD, also demonstrated a reduction in MACE and hospitalisation for heart failure HR 0.67 [95% CI 0.52, 0.87].[4] The Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial which compared dapagliflozin versus placebo in individuals generally of lower CV risk also found a lower risk of hospitalisation for heart

failure but no difference in MACE.[5] (Fig. 2) Real-world evidence also supports the findings from randomised controlled trials. The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors (CVD-REAL 2) study compared outcomes of patients initiated on SGLT2 inhibitors versus other GLDs in six countries in the Asia Pacific, the Middle East and North America regions. The use of SGLT2 inhibitors was associated with a 50% lower risk of death and 40% lower risk of hospitalisation for heart failure.[6]

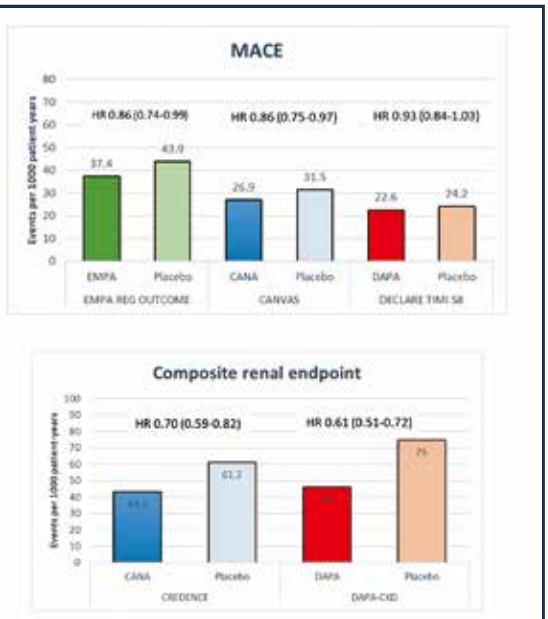


Fig. 2 Effects of SGLT2 inhibitors on major adverse cardiovascular events (MACE) and renal endpoints in randomised clinical trials
Comparison of empagliflozin (EMPA), canagliflozin (CANA) or dapagliflozin (DAPA) versus placebo on 3-point MACE and composite renal endpoints (sustained reduction in eGFR, end stage kidney disease or death from renal or cardiovascular causes) in phase 3 clinical trials. Expressed as events per 1000 patient-years and hazard ratio HR 95% CI.

SGLT2 INHIBITORS AND CKD PROGRESSION

The beneficial effects of SGLT2 inhibitors in preventing CKD progression in diabetes are now confirmed in a series of randomised controlled studies with dedicated renal endpoints. In the EMPAREG OUTCOME trial, empagliflozin compared with placebo was associated with improved renal outcomes, with lower incidence in worsening of nephropathy in 12 vs 18% (HR 0.61, 95% CI 0.53, 0.70) among T2D patients with CKD.[7] The benefit was irrespective of baseline estimated glomerular filtration rate (eGFR) down to eGFR 30 ml/min/1.73m^2. Beneficial effects of SGLT2i were confirmed in the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study[8], which compared the use of canagliflozin versus placebo in T2D patients with albuminuric CKD (eGFR 30-90 ml/min/1.73m^2). The primary renal endpoint was reduced by 30% in the canagliflozin group as compared with those on placebo. In the Dapagliflozin and prevention of Adverse outcomes in chronic kidney disease (DAPA-CKD) trial, which included 4304 patients with or without diabetes, dapagliflozin was associated with a lower risk of composite renal endpoint of ≥50% eGFR decline, kidney failure or death (HR 0.61 95% CI 0.52-0.72, p<0.001).[9] Notably, the DAPA-CKD trial included patients with eGFR down to 25 ml/min/1.73m^2 which confirms the safety and efficacy of SGLT2i in advanced CKD. A summary of these trials is shown in Fig. 2.

USE OF SGLT2 INHIBITORS IN NON-DIABETIC POPULATIONS

Non-diabetic Heart Failure

The observed differences in heart failure and survival occurred within months of SGLT2 inhibitor initiation and were largely independent of glucose-lowering effects. The exact mechanism by which SGLT2 inhibitors improve heart failure outcomes remains unclear, although changes in haemodynamic effects, osmotic diuresis, changes in cardiac substrate utilisation have been postulated as possible explanations.[10,11] The role SGLT2 inhibitor use in heart failure patients without diabetes has been evaluated. The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial recruited 4744 patients with reduced ejection fraction, including 50% of the participants who did not have diabetes at baseline. In this study, similar reductions in heart failure hospitalisation and mortality were observed in individuals with and without diabetes.[12] In another trial which compared empagliflozin versus placebo in heart failure patients with reduced ejection fraction, cardiovascular death or hospitalisation due to worsening heart failure was reduced by 25% in the empagliflozin group.[13] Again, the magnitude of reduction was similar in those with and without diabetes.

Non-diabetic CKD

Glomerular hyperfiltration is not unique to the diabetic state and occur in other causes of CKD. Patients with CKD have reduced nephron mass. The single nephron may undergo structural hypertrophy leading to single nephron hyperfiltration.[1] In the DAPA-CKD trial which included non-diabetic CKD patients, the relative risk reduction for the primary composite renal outcome with dapagliflozin was consistent in participants with type 2 diabetes (hazard ratio [HR] 0.64, 95% CI 0.52-0.79) and those without diabetes (0.50, 0.35-0.72). Consistent benefits of dapagliflozin were observed in patients with glomerulonephritides, ischemic or hypertensive CKD or secondary to unknown causes.[14]

Non-alcoholic Fatty Liver Disease (NAFLD)

Another emerging area is the use of SGLT2 inhibitors in NAFLD. NAFLD is common among individuals with T2D and is associated with the development of hepatic steatosis and non-alcoholic steaotohepatitis (NASH). SGLT2 inhibitors have been shown to reduce liver fat[14] in rodent models.[15,16] Greater reductions in alanine

EVENITY®
(romosozumab)
Solution for Injection
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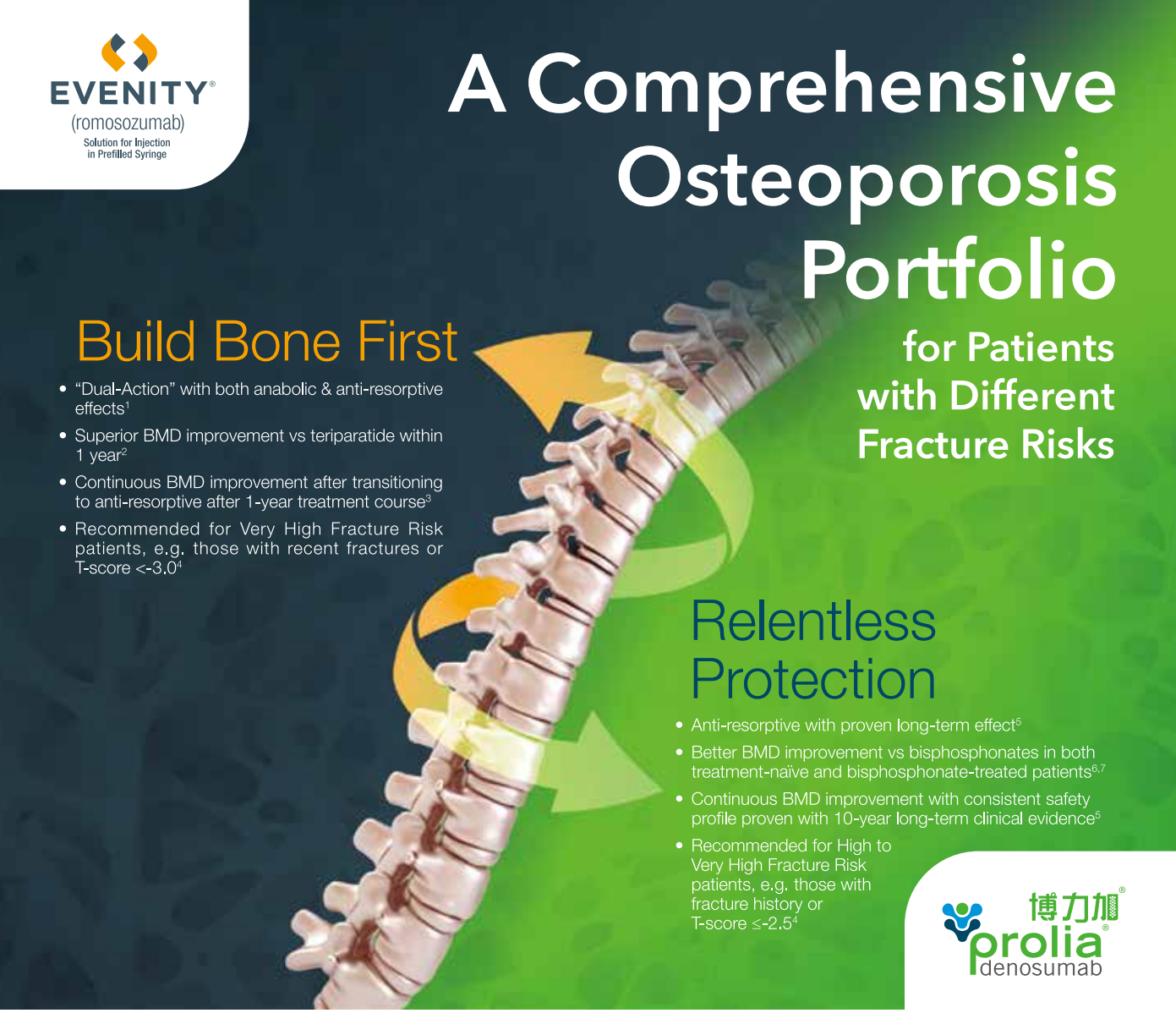
A Comprehensive Osteoporosis Portfolio

for Patients with Different Fracture Risks



Build Bone First

- "Dual-Action" with both anabolic & anti-resorptive effects[1]
- Superior BMD improvement vs teriparatide within 1 year[2]
- Continuous BMD improvement after transitioning to anti-resorptive after 1-year treatment course[3]
- Recommended for Very High Fracture Risk patients, e.g. those with recent fractures or T-score <-3.0[4]

Relentless Protection

- Anti-resorptive with proven long-term effect[5]
- Better BMD improvement vs bisphosphonates in both treatment-naïve and bisphosphonate-treated patients[6,7]
- Continuous BMD improvement with consistent safety profile proven with 10-year long-term clinical evidence[5]
- Recommended for High to Very High Fracture Risk patients, e.g. those with fracture history or T-score ≤-2.5[4]

博力加®
prolia®
denosumab

References:

1. Evenity Hong Kong Prescribing Information. Mar 2020. **2.** Langdahl BL, et al. Lancet 2017;390:1585–94. **3.** Saag KG, et al. N Engl J Med 2017;377:1417–27. **4.** Camacho P, et al. Endocr Pract 2020;26:1–46. **5.** Bone HG, et al. Lancet Diabetes Endocrinol 2017;5:513–23. **6.** Kendler DL, et al. J Bone Miner Res 2010;25:72–81. **7.** Brown JP, et al. J Bone Miner Res 2009;24:153–61.

EVENITY® (Romosozumab) Abbreviated Prescribing Information

EVENITY® Solution for Injection in Prefilled Syringe 105 mg/1.17 ml

INDICATIONS EVENITY is indicated in treatment of severe osteoporosis in postmenopausal women at high risk of fracture. **DOSAGE AND ADMINISTRATION** The recommended dose is 210 mg romosozumab (administered as two subcutaneous injections of 105 mg each) once monthly for 12 months. Patients should be adequately supplemented with calcium and vitamin D before and during treatment. Following completion of romosozumab therapy, transition to antiresorptive therapy is recommended in order to extend the benefit achieved with romosozumab beyond 12 months. Missed doses: If the romosozumab dose is missed, administer as soon as it can be feasible. Thereafter, the next romosozumab dose should not be given earlier than one month after the last dose. Elderly: No dose adjustment is necessary in elderly patients. Renal impairment: No dose adjustment is required in patients with renal impairment. Serum calcium should be monitored in patients with severe renal impairment or receiving dialysis. Hepatic impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment. Paediatric population: The safety and efficacy of romosozumab in paediatric patients (age <18 years) have not yet been established. No data are available. Method of administration: Subcutaneous use. To administer the 210 mg dose, 2 subcutaneous injections of romosozumab should be given into the abdomen, thigh, or upper arm. The second injection should be given immediately after the first one but at a different injection site. Administration should be performed by an individual who has been trained in injection techniques. **CONTRAINDICATIONS** Hypersensitivity to the active substance(s) or to any of the excipients. Hypocalcaemia. History of myocardial infarction or stroke. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Myocardial infarction and stroke: In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls. When determining whether to use romosozumab for an individual patient, consideration should be given to her fracture risk over the next year and her cardiovascular risk based on risk factors (e.g. established cardiovascular disease, hypertension, hyperlipidaemia, diabetes mellitus, smoking, severe renal impairment, age). Romosozumab should only be used if the prescriber and patient agree that the benefit outweighs the risk. If a patient experiences a myocardial infarction or stroke during therapy, treatment with romosozumab should be discontinued. Hypocalcaemia: Transient hypocalcaemia has been observed in patients receiving romosozumab. Hypocalcaemia should be corrected prior to initiating therapy with romosozumab and patients should be monitored for signs and symptoms of hypocalcaemia. If any patient presents with suspected symptoms of hypocalcaemia during treatment, calcium levels should be measured. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 ml/min/1.73 m2) or receiving dialysis are at greater risk of developing hypocalcaemia and the safety data for these patients is limited. Calcium levels should be monitored in these patients. Hypersensitivity: Clinically significant hypersensitivity reactions, including angioedema, erythema multiforme, and urticaria occurred in the romosozumab group in clinical trials. If an anaphylactic or other clinically significant allergic reaction occurs, appropriate therapy should be initiated and use of romosozumab should be discontinued. Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ), has been reported rarely in patients receiving romosozumab. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with romosozumab. Patients who are suspected of having or who develop ONJ while on romosozumab should receive care by a dentist or an oral surgeon with expertise in ONJ. Discontinuation of romosozumab therapy should be considered until the condition resolves and contributing risk factors are mitigated where possible. Atypical femoral fractures: Atypical low-energy or low trauma fracture of the femoral shaft, which can occur spontaneously, has been reported rarely in patients receiving romosozumab. Any patient who presents with new or unusual thigh, hip, or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of romosozumab therapy should be considered, based on an individual benefit-risk assessment. Sodium content: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium-free. **INTERACTIONS** No drug interaction studies have been performed with romosozumab. No pharmacokinetic drug interactions are expected with romosozumab. **PREGNANCY AND LACTATION** Pregnancy: Romosozumab is not indicated for use in women of child-bearing potential or in pregnant women. There are no data from the use of romosozumab in pregnant women. A risk for malformations of developing digits in the human foetus is low following romosozumab exposure due to the timing of digit formation in the first trimester in humans, a period when placental transfer of immunoglobulins is limited. Breast-feeding: Romosozumab is not indicated for use in breast-feeding women. No data are available on excretion of romosozumab in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Fertility: No data are available on the effect of romosozumab on human fertility. Animal studies in female and male rats did not show any effects on fertility endpoints. **ADVERSE REACTIONS** The most common adverse reactions were nasopharyngitis (13.6%) and arthralgia (12.4%). Hypersensitivity-related reactions occurred in 6.7% of patients treated with romosozumab. Hypocalcaemia was reported uncommonly (0.4% of patients treated with romosozumab). In randomised controlled studies, an increase in serious cardiovascular events (myocardial infarction and stroke) has been observed in romosozumab treated patients compared to controls. Adverse reactions are presented in order of decreasing seriousness by System Organ Class: Infections and infestations: Nasopharyngitis, Sinusitis; Immune system disorders: Hypersensitivity, Rash, Dermatitis, Urticaria, Angioedema, Erythema multiforme; Metabolism and nutrition disorders: Hypocalcaemia; Nervous system disorders: Headache, Stroke; Eye disorders: Cataract; Cardiac disorders: Myocardial infarction; Musculoskeletal and connective tissue disorders: Arthralgia, Neck pain, Muscle spasms; General disorders and administration site conditions: Injection site reactions **OVERDOSE** There is no experience with overdose in clinical trials.

Abbreviated Prescribing Information Version No.: HKEVEP01

Please read the full prescribing information prior to administration and full prescribing information is available upon request.

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Prolia® (Denosumab) Abbreviated Prescribing Information

Prolia® (denosumab) Solution for Injection in Pre-filled Syringe 60 mg/mL

INDICATIONS Prolia is indicated for: i) treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; ii) treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; iii) treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy; iv) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures; v) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. **DOSAGE AND ADMINISTRATION** The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. **CONTRAINDICATIONS** Hypocalcemia and pregnancy, as well as hypersensitivity to any component of the product. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Hypersensitivity: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritis, and urticaria. Hypocalcemia and Mineral Metabolism: Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis. Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Adequately supplement all patients with calcium and vitamin D. Osteonecrosis of the Jaw (ONJ): ONJ has been reported in patients receiving Prolia. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to Prolia treatment. Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain. Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment: Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. If Prolia treatment is discontinued, patients should be transitioned to an alternative antiresorptive therapy. Serious Infections: Serious infections leading to hospitalization were reported in clinical trial. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. Dermatologic Adverse Reactions: Dermatitis, eczema, and rashes. Most of these events were not specific to the injection site. Consider discontinuing Prolia if severe symptoms develop. Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain. Consider discontinuing use if severe symptoms develop. Suppression of Bone Turnover: In clinical trials treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. Osteonecrosis of the external auditory canal: Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. **PREGNANCY AND LACTATION** Pregnancy: Contraindicated. Breast-feeding: No information regarding the presence of denosumab in human milk, the effects on the breastfed infant, or the effects on milk production **PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT** Pediatric: Prolia is not recommended in pediatric patients younger than age 4 years. Geriatric: No overall differences in safety or efficacy were observed in clinical studies between elderly patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Renal Impairment: No dose adjustment is necessary in patients with renal impairment. **UNDESIRABLE EFFECTS** The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. The most common adverse reactions reported with Prolia in patients with glucocorticoid-induced osteoporosis are back pain, hypertension, bronchitis, and headache. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation. **OVERDOSE** There is no experience with overdosage with Prolia.

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transaminase (ALT) in empagliflozin treated patients were in the EMPAREG OUTCOME trial, independent of weight and HbA1c reduction.[17] Several studies have since investigated the effect of SGLT2i use on liver fat and fibrosis. In a small study of 50 type 2 patients with NAFLD, liver fat as detected by magnetic resonance imaging decreased from 16% to 11% treated among patients treated empagliflozin after 20 weeks.[18]

ADVERSE EFFECTS OF SGLT2 INHIBITORS

The most common side effect of SGLT2 inhibitors are genitourinary infections due to increased glycosuria. Uncomplicated infections uncomplicated infections can mostly be managed routinely[3]. Postural hypotension and volume depletion may also occur. A higher risk of lower-extremity amputation has been reported in the CANVAS programme among those receiving canagliflozin, as compared with placebo (HR 1.97, 95% CI 1.41, 2.75).[4] However, this has not been reported with other SGLT2 inhibitors. Patients reated with SGLT2 inhibitors are at increased risk of diabetic ketoacidosis (DKA) which can occur within the euglycaemic range. Stress and starvation may tip the balance towards ketone production, especially in patients with relative insulin deficiency, while the glycosuric effects of SGLT2 inhibitors continue to keep glucose in an apparently normal range. In the CANVAS study, the risk of DKA was two-fold higher in the canagliflozin treated arm as compared with placebo (0.6 versus 0.3 per 1000 patient-years, HR 2.33 95% CI 0.76, 7.17).[4] For these reasons, SGLT2 inhibitors should be discontinued during acute illness and at least 48 hours before operative procedures.[3] Patients should be appropriately advised on these precautions.

CONCLUSION

The latest international guidelines recommend SGLT2 along with glucagon-like peptide-1 receptor agonists after first-line metformin therapy in type 2 diabetes patients at high atherosclerotic CVD risk, CKD or with heart failure.[19] The role of SGLT2 inhibitor as an organ-protective drug for type 2 diabetes is established and supported by trial and real-world evidence. SGLT2 inhibitors will increasingly be used beyond their original glucose lowering indication. We anticipate cardiology and nephrology communities to be adopting these therapies to benefit a wider range of heart failure and CKD patients with and without diabetes in the future.

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COVID-19 Vaccine Allergy Safety in Hong Kong

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BACKGROUND

Coronavirus disease 2019 (COVID-19) has been responsible for the deaths of more than 4 million individuals and has caused irreparable damage to the society. Achieving herd immunity is currently the most promising anti-COVID-19 strategy to finally instigate the end of the pandemic. Since February 2021, Hong Kong has run a territory-wide COVID-19 vaccination programme, providing her residents with two vaccines the Sinovac CoronaVac and the Fosun Pharma BioNTech Comirnaty.

Despite the generally proven safety of the vaccinations, the overall vaccine acceptance rate was below 40% even before the commencement of Hong Kong's COVID-19 vaccination programme[1,2]. This correlated with the perceived harm of COVID-19 vaccination, as well as the lack of trust in the healthcare system. Soon after the initial rollout, reports of suspected anaphylaxis and severe allergic reactions to the COVID-19 vaccination rapidly dominated news reports, creating major safety concerns and vaccine hesitancy. Worringly, most reported cases seemed to occur following first dose COVID-19 vaccination and was thought to be due to allergy to excipients found in mRNA vaccines (such as polyethylene glycol [PEG] found in Fosun Pharma BioNTech Comirnaty).

LOCAL RECOMMENDATIONS FOR COVID-19 VACCINE ALLERGY SAFETY

In response to concerns regarding COVID-19 vaccine allergy safety (VAS), the Hong Kong Institute of Allergy (HKIA) issued its first set of consensus statements on the approach of COVID-19 VAS in April 2021[3]. With accumulation of both local and international experience regarding COVID-19 VAS, this was superseded by an updated consensus statements published in September 2021[4]. The objectives of the statements were to define those people at higher risk of potential COVID-19 vaccine-associated allergies, and to highlight the importance of pre-vaccination and post-vaccination assessment by frontline healthcare workers and evaluation by specialists (Fig. 1). Both the original and updated consensus statements have also been adopted by the Department of Health[5]. Individuals deemed to be at higher risk of COVID-19 vaccine-associated allergic reactions were recommended to defer COVID-19 vaccination until physician assessment, and, if deemed necessary, they can be referred for formal Allergist assessment to exclude potential COVID-19 vaccine or excipient-associated allergies.

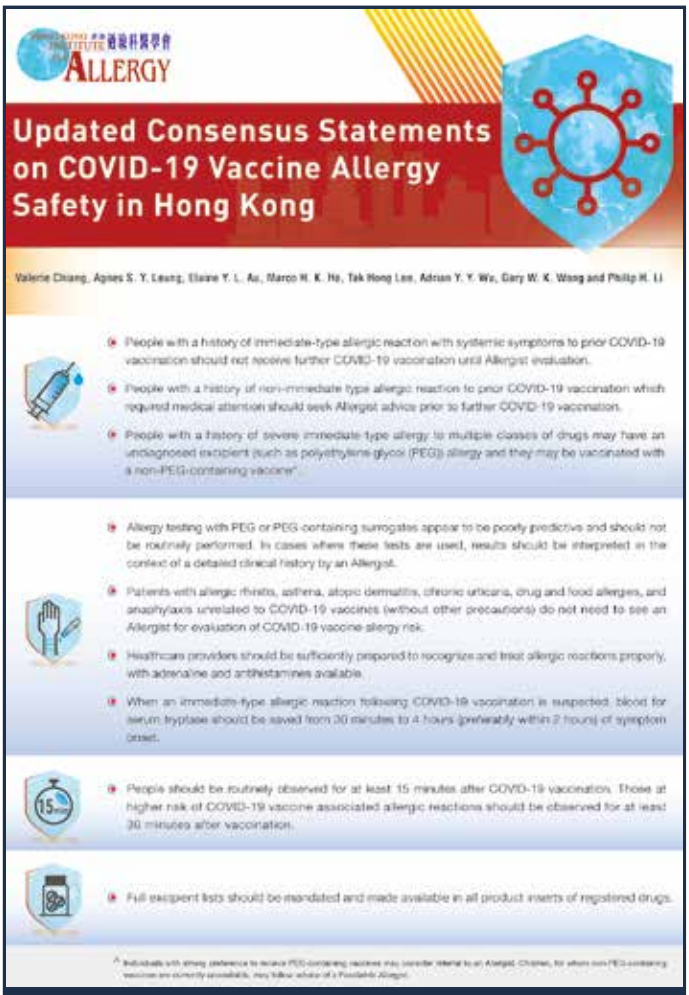

Fig. 1: Updated Consensus Statements on COVID-19 Vaccine Allergy Safety in Hong Kong (Adopted from [4])

BALANCE BETWEEN VACCINE SAFETY AND UPTAKE

The HKIA VAS consensus statements proved to be successful in maintaining a low rate of COVID-19 vaccine-associated allergies in Hong Kong. As of Aug 2021, there have only been four confirmed cases of anaphylaxis (fewer than 0.5 cases per million doses

administered), which is much lower than incidences recorded in other countries[6-9]. However, there remains a balance between maintaining vaccine safety and promoting vaccine uptake.

To tackle the issue of COVID-19 VAS, the University of Hong Kong (HKU) and the Hospital Authority Hong Kong West Cluster (HKWC) have set up a dedicated VAS Clinic since March 2021. Specialists in the private sector have also set up dedicated services for COVID-19 vaccine allergy testing. However, with a shortage of Specialists in Immunology & Allergy in Hong Kong, it has been an overwhelming challenge to see and assess all referred patients in time, resulting in long waiting times and delays in vaccinations[10]. At the time of writing, the HKU/HKWC VAS Clinic runs at least three times per week but has received more than 2,500 new referrals in June 2021 alone. The waiting time for an appointment at VAS Clinic reached more than 7 years and led to a surge in public dissatisfaction. In response to this, the Hospital Authority established 7 new inter-disciplinary VAS Clinics across Hong Kong under its new "Hub-and-Spoke" allergy service model. Each of the 7 geographical territories under the Hospital Authority (clusters) had 1 "spoke" VAS Clinic, supported by the HKWC/HKU Immunology & Allergy team acting as the "Hub".

INAPPROPRIATE REFFERALS, INACCURATE DIAGNOSES AND URGENT NEED TO STRENGTHEN ALLERGY SERVICES IN PRIMARY CARE

The HKU/HKWC VAS Clinic received a total of 3,940 referrals between March to June 2021, but fewer than 15% of these patients have been seen due to limitations of manpower. In order to help shorten the waiting time, a protocol-based pre-consultation assessment has been instigated to help triage patients before attending the VAS Clinic. Worryingly, up to 45% of referrals were identified as inappropriate due to insufficient information or incorrect indications for referral (i.e., did not meet HKIA criteria for COVID-19 VAS evaluation). Furthermore, out of more than 180 patients who were referred for the history of suspected "anaphylaxis" (a precaution listed in the first version of the HKIA consensus statements[3]), only 44% of them were found to actually fulfill anaphylaxis diagnostic criteria (i.e., 56% of patients diagnosed with "anaphylaxis" by their referring doctors were incorrectly diagnosed). If we extrapolate inappropriate referrals and incorrect diagnoses of anaphylaxis alone, we could easily have directed more than half of all patients to vaccination without the need for prior Allergist evaluation!

The success of the COVID-19 vaccination programme will rely on all our medical professionals, and this step of risk-stratification and prevention of unnecessary delays in vaccination heavily depends on the physicians initially evaluating a patient's allergy history. In the vast majority of cases, primary care and family physicians should be able to make the appropriate judgment call based on objective clinical criteria provided by the HKIA recommendations. There is a dire need for further interdisciplinary collaboration and strengthening of Allergy services in primary care.

MORE THAN 97% OF HIGH RISK PATIENTS PROCEED WITH COVID-19 VACCINATION AFTER EVALUATION

In our experience, even among patients who were deemed at higher risk of COVID-19 vaccine-associated allergic reactions, only 2.4% of these patients were advised to defer COVID-19 vaccination following Allergist review (Fig. 2). The remaining patients were recommended to proceed with COVID-19 vaccination. Post-consultation telephone interviews confirm that around 80% of patients followed our advice and were vaccinated uneventfully, but around 20% have yet to book their vaccinations.

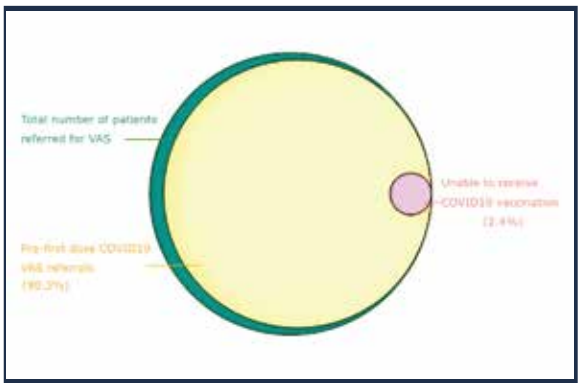

Fig. 2: Breakdown of referrals and outcomes of HKU/HKWC VAS Clinic
(Unpublished data; from HKWC/HKU VAS Clinic)

URGENT CALL FOR PHARMACEUTICAL LEGISLATION REFORM

Out of the 2.4% of patients advised to have their vaccination deferred, the majority had potential excipient allergies that could not be excluded. Currently, registered drugs in Hong Kong are still not mandated to include excipient lists in product inserts. Therefore, without being able to identify culprit excipients, excipient allergies remain almost impossible to diagnose, and some patients cannot be confidently deemed safe for vaccination. In response to this, the HKIA Updated Consensus Statements on the Approach to COVID-19 Vaccine Allergy Safety in Hong Kong now advocate administration of non-PEG containing vaccines for patients with possible excipient allergies.

However, this approach is far from ideal. We echo the HKIA consensus statements and implore that full excipient lists for all registered drugs should be mandated in Hong Kong as soon as possible[3]. In the interim, at least a comprehensive list of drug formulations containing excipients shared by the COVID-19 vaccines should also be made readily accessible for cross-referencing for physicians.

CONCLUSION

Achieving herd immunity in Hong Kong should be made an urgent priority. It is imperative that patients should not be inappropriately excluded from vaccination but equally important that the public maintains confidence in vaccination safety. Appropriate VAS guidance is essential to maintain low anaphylaxis rates, and yet such guidance should not become a barrier to vaccination uptake. Barriers to VAS include a high proportion of inappropriate referrals, inaccurate diagnosis of anaphylaxis, and inability to diagnose excipient allergies. Closer collaboration between primary care doctors and Allergy specialists should be fostered. Furthermore, relevant changes in pharmaceutical legislation should be made a priority to promote drug and vaccine allergy safety.

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FOURIER study design: The FOURIER study was a double-blind, randomized, placebo-controlled, event-driven trial in 27,564 adult subjects with established CVD and with LDL-C 1.8 mmol/L and/or non-HDL-C 2.6 mmol/L despite high- or moderate-intensity statin therapy. Subjects were randomly assigned to receive Repatha® (140 mg every 2 weeks or 420 mg once monthly) or placebo. The median follow-up duration was 26 months.[1] The risk of the primary efficacy endpoint (a composite endpoint of time to CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization) was reduced by 15% (HR: 0.85; 95% CI: 0.79–0.92; p<0.001).[1]

OSLER-1 study design: OSLER-1 was an open-label, 4-year extension study following a 1-year randomized treatment period.[2] 1,125 subjects enrolled in one of five phase 2 studies of Repatha® were randomized to SOC or SOC plus Repatha® 420 mg monthly during the randomized period; 1,151 patients progressed to the all-Repatha® period (420 mg monthly, plus SOC) for year 2 and beyond.[2] The primary objective was characterization of the long-term safety and tolerability of Repatha®; subjects were followed for up to 5 years.[2]

Abbreviations
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; MI, myocardial infarction; RRR, relative risk reduction; SOC, standard of care.

Repatha® (Evolocumab) Abbreviated Prescribing Information
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INDICATIONS Hypercholesterolaemia and mixed dyslipidaemia: Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet: in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. Homozygous familial hypercholesterolaemia: Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies. Established atherosclerotic cardiovascular disease: Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. **DOSAGE AND ADMINISTRATION** Primary hypercholesterolaemia and mixed dyslipidaemia in adults: The recommended dose of evolocumab is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent. Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over: The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule. Established atherosclerotic cardiovascular disease in adults: The recommended dose of evolocumab is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent. No dose adjustment is necessary in elderly patients. No dose adjustment is necessary in patients with renal impairment. No dose adjustment is necessary in patients with mild hepatic impairment. The safety and efficacy of Repatha in children aged less than 18 years has not been established in the indication for primary hypercholesterolaemia and mixed dyslipidaemia. The safety and efficacy of Repatha in children aged less than 12 years has not been established in the indication for homozygous familial hypercholesterolaemia. Evolocumab is for subcutaneous injection into the abdomen, thigh or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard. Evolocumab must not be administered intravenously or intramuscularly. The 420 mg dose should be delivered using three pre-filled autoinjectors administered consecutively within 30 minutes. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Hepatic impairment: In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL C reduction. Therefore, close monitoring may be warranted in these patients. Patients with severe hepatic impairment (Child-Pugh C) have not been studied. Evolocumab should be used with caution in patients with severe hepatic impairment. Dry natural rubber: The needle cover of the pre-filled autoinjector is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions. Sodium content: This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'. **INTERACTIONS** An approximately 20% increase in the clearance of evolocumab was observed in patients co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of evolocumab on lipids. No statin dose adjustments are necessary when used in combination with evolocumab. **PREGNANCY AND LACTATION** Pregnancy: There are no or limited amount of data from the use of Repatha in pregnant women. Repatha should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. Breast-feeding: It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Repatha therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Fertility: No data on the effect of evolocumab on human fertility are available. **ADVERSE REACTIONS** The most commonly reported adverse reactions, at the recommended doses, are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%). The safety profile in the homozygous familial hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia population. Adverse reactions reported in pivotal, controlled clinical studies, and spontaneous reporting, are displayed by system organ class and frequency below: *Infections and infestations:* Influenza, Nasopharyngitis, Upper respiratory tract infection (Common); Immune system disorders: Hypersensitivity, Rash (Common), Urticaria (Uncommon); Gastrointestinal disorders: Nausea (Common); *Skin and subcutaneous tissue disorders:* Angioedema (Rare); *Musculoskeletal and connective tissue disorders:* Back pain, Arthralgia (Common); *General disorders and administration site conditions:* Injection site reactions (Common), Influenza-like illness (Uncommon). The most frequent injection site reactions were injection site bruising, erythema, haemorrhage, injection site pain, and swelling. Paediatric population: There is limited experience with evolocumab in paediatric patients. No difference in safety was observed between adolescent and adult patients with homozygous familial hypercholesterolaemia. The safety and effectiveness of evolocumab in paediatric patients with primary hypercholesterolaemia and mixed dyslipidaemia has not been established. Elderly population: No overall differences in safety or efficacy were observed between these patients and younger patients. Immunogenicity: The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of evolocumab. **OVERDOSE** No adverse effects were observed in animal studies at exposures up to 300 fold higher than those in patients treated with 420 mg evolocumab once monthly. There is no specific treatment for evolocumab overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

Abbreviated Prescribing Information Version: HKREPPI04
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HK-04745-REP-2020-Sep

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Safe Use of Chemical Restraint for Agitated and Violent Adult Patients

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INTRODUCTION

Agitation and aggression are common reasons for hospital attendance with escorts by law enforcement officers. Intoxications, psychosis, behavioural and psychological symptoms of dementia, traumatic brain injury, and medical problems (such as hypoglycaemia, electrolyte disturbance, sepsis, intractable pain, and acute urinary retention) are common correlations. They impose threats to the physical, psychological, and emotional wellbeing of the patient and attending staff.

BURDEN OF WORKPLACE VIOLENCE IN HEALTHCARE SETTINGS

In Hong Kong, healthcare workers frequently reported to the police for workplace violence, second to police officers.[1] Among 400 to 500 reported cases of workplace violence in public health facilities annually, 22.1% involved threats, intimidation or aggressive behaviours, and 16.4% involved physical assault. More than 350 healthcare workers sustained physical and non-physical injuries. The three commonest medical specialities were Psychiatry units, Emergency departments, and Internal Medicine units. Nurses were the most vulnerable.[2] While observing human rights and patient's best interests, the healthcare team should take on emergency behavioural management in order to protect the patient and the staff, and to avoid interruption of important treatment. Emergency behavioural management conventionally adopts a stepwise approach, from de-escalating "talk-down", seclusion in a quiet room in dim lighting, to the use of physical and chemical restraints.

EXCITED DELIRIUM IS A MEDICAL EMERGENCY

Excited delirium with intense mental and physiological excitement is a medical emergency, and is characterised by extreme agitation, hyperthermia, hostility, exceptional strength, and endurance without apparent fatigue.[3] It carries a mortality of 8.3 - 16.5%, notably acute myocardial infarction, which demands high diagnostic vigilance and time-sensitive medical intervention.[4] Proposed mechanisms of sudden death include dopaminergic overdrive, autonomic dysregulation, hyperthermia, rhabdomyolysis, cardiac arrhythmia, and impaired respiratory mechanics.[5] The underlying causes are myriad and possibly time-consuming to identify. Non-pharmacological interventions are often inadequate. Chemical restraint is the reasonable next step to mitigate dopaminergic overdrive and circumvent metabolic acidosis.

CHEMICAL RESTRAINT – WHAT IS IT AND WHY BOTHER?

Chemical restraint is a pharmacological intervention to moderate patient behaviour, by transiently restricting freedom of movement. It is used in an emergency when confronted with an imminent risk of violence, especially involving weapons. It is just a means to an end – to buy time for safe physical assessments and investigations (e.g. blood and urine sampling, lumbar puncture, computed tomography scan of the brain), or to continue supportive care while awaiting wearing off of a stimulant medication.

This article focuses on the use of chemical restraint for adult patients who are not well known to the clinicians in healthcare settings. It is recognised that psychiatrists have more experience in managing patients with psychiatric conditions, and they may choose agents for chemical sedation other than those described below.

SAFE PRACTICE OF PHYSICAL AND CHEMICAL RESTRAINTS

Decision on and application of restraint is a shared-care process involving both doctors and nurses. On some occasions, physical restraints are decided on and applied as a nurse-initiated intervention out of urgency. Soon afterwards, doctors should be called in to assess in person and to consider chemical restraint in tandem. Applying restraint is often perceived as an infringement of personal freedom. Therefore, reasons for such orders should be documented clearly in the medical notes, instead of "restrain prn". The need for restraint should be explained to patient and relatives, preferably supplemented by a fact sheet.

ISOLATED USE OF PHYSICAL RESTRAINTS IS NOT IDEAL

Healthcare providers are often tempted to apply physical restraint upfront to restrict patient movements. However, it may cause false reassurance to the treating

team that the problem has been solved instead of addressing the underlying pathology. The deleterious effects of physical restraints include falls, injuries, incontinence, circulation impairment, agitation, social isolation, and death.[6] Patients with excited delirium may exhibit superhuman strength and appear impervious to pain. Struggling against physical restraints in a state of pain unawareness may cause excessive stress to musculoskeletal structures. It is associated with fracture, dislocation, rhabdomyolysis, strangulation, aspiration, asphyxiation, respiratory arrest, and death.

PROS AND CONS OF CHEMICAL RESTRAINT

Under proper administration and monitoring, the addition of a chemical restraint to an agitated patient offers a few advantages. Chemical restraint improves patient comfort by anxiolysis while buying time for laboratory results and wear-offs from toxic substances (e.g. stimulants). It may obviate the need for, or reduce the intensity of, physical restraints.

Chemical restraint may sometimes paradoxically worsen delirium, in particular for the elderly receiving benzodiazepine, and children receiving ketamine. Drug accumulation secondary to reduced clearance may cause inadvertent over-sedation or other toxic effects. Clinicians should aim to calm rather than to sedate acutely agitated patients.[7] The ultimate goal is to restore self-control capacity, by reducing hyperarousal as rapidly and safely as possible.[8]

PATIENT-BASED APPROACH TO CHEMICAL RESTRAINT

It is pivotal to rapidly identify and correct the readily treatable causes of agitation and aggression. All patients should be rapidly screened for hypoglycaemia, electrolyte imbalance, acute urinary retention, and traumatic brain injury. An efficient approach is perhaps to start initial treatment and address the provisional diagnosis at the same time. The selection of pharmacological agents and route of administration should be based on balancing risks and benefits in the patient's context (Tables 1 and 2). Intramuscular benzodiazepines or olanzapine are the preferred initial agents for the treatment of acute undifferentiated agitation.[11] Benzodiazepines are preferred to other antiepileptics for drug-induced seizure. Olanzapine and haloperidol can treat hallucinations related to acute psychosis. Ancillary therapies should be considered for specific conditions (Table 3).

Table 1. Routes to administer sedatives

Route	When	Pros	Cons
Oral	- Alert - Patent airway - Intact gag reflexes - No vomiting - Cooperative	- Non-invasive - Less coercive and abusive as perceived by the patient[9]	- Low oral bioavailability (15-27% for midazolam)[10] - Onset of action dependent on gastric emptying, absorption, first-pass effect
Rectal (mostly diazepam)	- Drug-induced seizure - Prehospital - IV access is not available - Young child	- Does not require IV catheterisation - Avoids needlestick injury, especially while seizing	- Erratic drug absorption - Less predictable dose-response relationship - Rectal perforation
Intramuscular	- Prehospital - IV access is not available - Uncooperative	- Does not require IV catheterisation which can be difficult in an uncooperative patient	- May be perceived as assault and not welcomed
Intravenous (peripheral line at first)	- Route of choice for most in-hospital settings (emergency departments, wards, psychiatric units) - Uncooperative patient	- Rapid onset (~20 sec arm-to-brain circulation time) - Titratable doses can be administered - Repeated boluses - Infusion with adjustable rates (e.g. midazolam, dexmedetomidine)	- May be perceived as assault and not welcomed - Difficult to establish IV access when violent - Heparin lock/ catheter dislodgement - Thrombophlebitis - Bleeding - Pressure injury - Infusion pump necessary for sedative infusion - Easily overshoot
Inhalational	- Post-operative (emergence agitation) - Intensive care units - Dental procedural sedation - Cooperative patient	- Rapid onset (< 20 sec pulmonary circulation to brain time) - Short time to peak clinical effect - Depth of sedation easily controllable - Rapid offset (complete recovery after inhaling 100% oxygen for 3 - 5 min) - No needles	- Cost - Space occupying, fixed equipment - Cannot be used in uncooperative patients - Leakage of gas causes occupational hazard - Expertise not available in emergency department, Psychiatric units, general wards
Intranasal (via atomiser)	- Prehospital - Procedural sedation (e.g. close reduction of joint after seizure)	- Rapid onset - Avoids needles - Non-invasive - Technically easy to administer - No first-pass effect	- Atomiser is not widely available - Interference by nasal congestion and bleeding - In small volumes only - Mucosal damage

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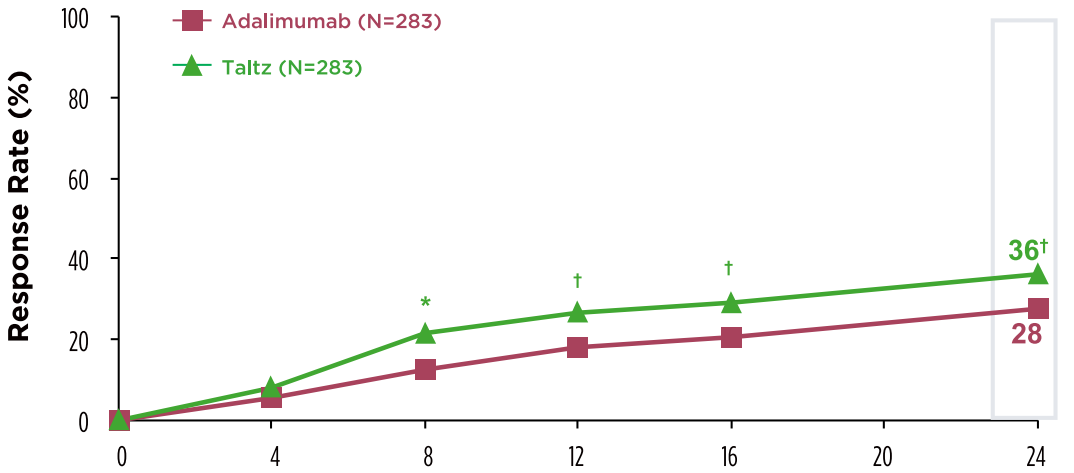
SPIRIT H2H (BIOLOGIC NAÏVE): PERCENTAGE OF PATIENTS SIMULTANEOUSLY ACHIEVING

ACR 50 AND | **PASI 100 At WEEK 24, NRI**



* P<0.01 vs adalimumab at week 8. Onset of response was statistically significant higher as early as week 8 through to week 24.

† P<0.05 vs adalimumab at week 24.

All patients had BSA ≥3%; patients with BSA ≥10%, PASI ≥12, sPGA ≥3 followed the approved dosing for moderate to severe plaque psoriasis.

ACR50 = American College of Rheumatology response criteria with 50% improvement; BSA = body surface area; IL = interleukin; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; sPGA = static Physician Global Assessment.

Reference: Mease PJ, et al. Ann Rheum Dis. 2020;79:123-131.

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Table 2. Commonly used agents for chemical restraint

Agent	Mechanism of action	Starting dose (for agitated adult patient)	Onset	Duration of action	Remarks	
Benzodiazepine						
Midazolam	- Enhances binding of GABA to $GABA_A$ receptors - Increases frequency of chloride channel opening	2 - 5 mg IV every 3 - 5 min; 5 - 10 mg IM	< 5 min (IV); 5 - 15 min (IM)	30 - 80 min (IV); 1 - 2 h (IM)	- effective for motor agitation - short acting - greater sedation - commonly used as IV infusion	- respiratory depression - excessive somnolence - paradoxical disinhibition (uncommon)
Diazepam		5 - 10 mg IV/ PO; Every 3 – 5 min for IV	5 min (IV); 0.5 - 3 h (PO)	20 - 100 h	- long acting - better for withdrawals - prolonged sedation - not for IM (erratic effect, rise in creatine kinase) - oil based, painful injection	
Lorazepam		2 - 4 mg IV/ IM; Every 10 - 30 min for IV	5 - 10 min (IV); 30 - 45 min (IM)	2 - 6 h	- preferred benzodiazepine - complete and rapid IM absorption	
Antipsychotic						
Haloperidol	- "Typical" antipsychotic - Blocks dopamine D2 & D3, histamine and noradrenaline receptors	2.5 - 10 mg IM/ (IV)	15 - 60 min (IM)	12 - 48 h	- Less sedating than benzodiazepine - IV route is off-label use by FDA standard - Extrapyramidal effects (amendable to benztropine IM, benzhexol PO) - Neuroleptic malignant syndrome - prolonged QT interval	
Olanzapine	- "Atypical" antipsychotic - Blocks 5-HT_{2A}, 5-HT_{2C}, histamine-1, muscarinic M1-5 receptors	5 - 10 mg PO; 10 mg (IM)	15 - 45 min (IM)	Up to 24 h	- Less extrapyramidal symptoms - Excessive sedation - Reduced seizure threshold - Possible respiratory depression, hypotension (especially IM), bradycardia, syncope (caution for those with significant medical comorbidities)	
Phencyclidine derivative						
Ketamine	- Non-competitive NMDA receptor antagonist	1 mg/kg (IV); 5 mg/kg (IM)	1 - 2 min (IV); 3 min (IM)	0.5 - 2 h (IM)	- More rapid onset than antipsychotics - May not be adequate as a sole agent - Reserved for combative, excited delirium patients, either as first-line, or after treatment failures of benzodiazepine and antipsychotic - Reports of emergency intubation during procedural sedation but not excited delirium	
Centrally acting alpha-2 adrenergic receptor agonist						
Dexmedetomidine	- Centrally acting selective alpha-2 (subtypes A, B, C) agonist - Sedative-analgesic with sympatholytic property	Loading: 1 mcg/ kg IV over 10 min Maintenance: 0.2- 0.7 mcg/kg/h IV infusion (not longer than 24 h)	5 - 10 min	60 - 120 min	- Only licensed for up to 24 h of administration - Advantage of preserved respiratory drive during sedation - Reduces blood pressure and heart rate for stimulant intoxications - Candidate agent for switch therapy after high-dose benzodiazepines - Risks of hypotension, bradycardia, and sinus arrest (caution in advanced heart block and severe ventricular dysfunction)	

GABA: gamma-aminobutyric acid; IV: intravenous; IM: intramuscular; PO: oral; NMDA: N-methyl-D-aspartate; FDA: United States Food and Drug Administration

Table 3. Preferred therapies for specific conditions

Xenobiotic/ condition	Preferred therapy
Acute psychosis and mania	Antipsychotics
Chronic alcoholism	Thiamine, dextrose
Cyanide	Sodium nitrite & sodium thiosulphate; or hydroxocobalamin
Digoxin	Digoxin immune Fab (DigiFab®)
Drug-induced agitation (including Chinese medicine e.g. ma huang, ginseng, ephedra)	Benzodiazepines
Opiates	Naloxone
Sulfonylurea	Dextrose, octreotide (for refractory hypoglycaemia)
Toxic alcohols (e.g. methanol)	Ethanol, fomepizole, haemodialysis
Valproate	L-carnitine
Withdrawals	Benzodiazepines for benzodiazepine, zopiclone and alcohol withdrawals; Methadone for opiate withdrawal
Hyperthermia syndromes	
Anticholinergic delirium (e.g. scopolamine, *Datura* species)	Physostigmine (+/- benzodiazepine)
Malignant hyperthermia	Cooling, benzodiazepines, dantrolene
Neuroleptic malignant syndrome	Cooling, benzodiazepines, bromocriptine
Serotonin syndrome	Cooling, benzodiazepines, cyproheptadine
Sympathomimetic toxidrome	Benzodiazepines

Certain patient groups deserve special attention because of altered pharmacokinetics, pharmacodynamics, and risk of exposure to culprit agents. Elderly patients have more adipose tissue, such that the volumes of distribution and half-lives of lipophilic drugs increase. Slower renal clearance, reduced first-pass effect (increased oral bioavailability), and polypharmacy make elderly patients more prone to drug interactions and toxic effects. Chronic alcoholics are prone to thiamine deficiency and malnutrition. Bodybuilders may use androgenic-anabolic steroids, which could cause aggression. One should be cautious to avoid withdrawals when administering antidotes to patients with substance dependence, such as naloxone for opiates, and flumazenil for benzodiazepines. Chronic sedative users may require higher sedative doses during chemical restraint. Antipsychotics with the risk of prolonging QT interval should be avoided to sedate a patient on other QT-prolonging drugs. If possible, an electrocardiogram will be helpful to aid agent selection.

POST-RESTRAINT MANAGEMENT

Close monitoring of patient is needed to ensure safety when restraints are in place. Standards of personal care, including personal hygiene, nutrition, hydration, continence, turning, as well as protection against aspiration and deep vein thrombosis, should be upheld. Monitoring of vital signs, oxygen saturation, cardiac rhythm, fluid inputs and outputs, circulation, and neuro-observation should continue. The duration of restraints should be minimal. Hospital or clinical department-based clinical guidelines should be in place, subject to regular audits and reviews.[12,13]

Table 4. Common pitfalls during sedative administration

Pitfalls	Suggested solutions
Intravenous catheter-related complications: Kinking, dislodgement, pressure injury	- Avoidance of prolonged skin contact with the protruded part of catheter - Proper exposure of the exit site covered by water resistant transparent adhesive (e.g. Tegaderm®), surrounded by non-obscuring adhesive fabric (e.g. Mefix®) for site protection and regular assessment
Inadequate tranquillisation	- Ensure adequate dosage - Administer intravenous push bolus injections unless otherwise specified - Ensure sufficient intravenous line flush volume after each bolus: at least 10 - 20 mL 0.9% sodium chloride solution - Switching agents from one class to another, or combining more than one class of therapies
Fear of overshooting and under-sedation	Consider a stepwise approach of repeated boluses under close monitoring: Diazepam: 5 mg as the first bolus, followed by another 5 mg after 3 - 5 min, and then double the dose to 10 mg, as follows: 5 mg + 5 mg + 10 mg + 10 mg + 20 mg + 20 mg…. until desired response is achieved. The total dose of diazepam received to achieve the first successful sedation can be up to 50 - 100 mg in severe stimulant intoxications.
Forgot about other medical needs during chemical restraint	- Hypertension and tachycardia signal poor analgesia - Bear in mind that not all sedatives have analgesic property - Consider morphine/ fentanyl co-administration, especially for pain in withdrawal, delusional parasitosis in methamphetamine and cocaine intoxications - Routine input/ output charting
Incomplete documentation	- Use standard forms and checklists with structured formats; a good example is a resuscitation form which documents serial vital signs and medications with dose, route, and time. - Shared care team approach: endorsement by both nurses and doctors - Cross-checking while logging the drugs administered, particularly for items regulated under Dangerous Drugs Ordinance (Cap. 134)

CONCLUSION

Despite ongoing controversy, chemical restraint is a clinically important intervention for timely protection against self-harm and workplace violence. It should be considered early when physical restraint is applied. The selection of pharmacological agents and administration routes should be based on the clinical condition. Patient safety and rights should command top priorities.

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Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	* Certificate Course on Cardiology 2021 (Video Lectures) 5	* Zoom Lecture The Sweetspot for DM Management - What's the Role of SGLT2 Inhibitor? - Online * Certicifate course on Respiratory Medicine 2021 (Video Lectures) 6	* Zoom Lecture Updates on Menstrual Disorders Management - Hormonal Treatment and Myths - Online * Certificate Course on Renal Medicine 2021 (Video Lectures) 7	8	9
10	11	* Certificate Course on Cardiology 2021 (Video Lectures) 12	* Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures) * The Hong Kong Neurosurgical Society Monthly Academic Meeting 13	14	* Zoom Lecture Update in Management of Lung Cancer - Online 15	16
17	* Zoom Lecture In Search Of Completely Clear Skin – Findings On PASI 100 Results From Clinical Trials And Real Life In Plaque Psoriasis - Online 18	* Certificate Course on Cardiology 2021 (Video Lectures) 19	* Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures) 20	* Zoom Lecture The Role of Novel Antidepressants in Managing Major Depressive Disorder (MDD) - Online * FMSHK Executive Committee Meeting * FMSHK Council Meeting 21	* Zoom Lecture Nutrition Intervention for Type 2 Diabetes Mellitus (T2DM) Patients - Online 22	23
24		* Certificate Course on Cardiology 2021 (Video Lectures)	* Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures)	* Zoom Lecture Breakthrough in Heart Failure Management: The Latest Scientific Update - Online		
31	25	26	27	28	29	30

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Date	Topics	Speakers
9 November 2021	Early Language Development & Disorders	Dr. Anita Wong Associate Professor BSc (Speech and Hearing Sciences) Faculty of Education The University of Hong Kong
16 November 2021	Speech Sound Development & Disorders	Dr. Carol To Associate Professor Academic Unit of Human Communication, Development and Information Sciences Faculty of Education The University of Hong Kong
23 November 2021	Dyslexia	Dr. Dustin Lau Associate Professor Department of Chinese & Bilingual Studies Hong Kong Polytechnic University
30 November 2021	Bilingual Development in Children	Dr. Angel Chan Associate Professor Department of Chinese & Bilingual Studies Hong Kong Polytechnic University
7 December 2021	Understanding Developmental Stuttering in Children	Dr. Thomas Law Assistant Professor & Deputy Chief of Division Department of Otorhinolaryngology, Head and Neck Surgery The Chinese University of Hong Kong
14 December 2021	Aural Rehabilitation for Children with Hearing Impairment	Dr. Kathy Lee Associate Professor & Chief Division of Speech Therapy Department of Otorhinolaryngology, Head and Neck Surgery Faculty of Medicine The Chinese University of Hong Kong

Date : 9, 16, 23, 30 November & 7, 14 December 2021 (Every Tuesday)
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Date / Time	Function	Enquiry / Remarks
5 TUE 7:00 PM	**Certificate Course on Cardiology 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong College of Cardiology Speaker: Dr Ko Kwok Chun, Jason	Ms Vienna Lam Tel: 2527 8898
6 WED 2:00 PM	**Zoom Lecture** **The Sweetspot for DM Management - What's the Role of SGLT2 Inhibitor? - Online** Organiser: HKMA-Central, Western & Southern Community Network Speaker: Dr. TING Zhao Wei, Rose	Ms. Antonia Lee Tel: 2865 0943 1CME Point
7:00 PM	**Certicifate course on Respiratory Medicine 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong Thoracic Society Limited, Delegation Hong Kong and Macau Limited Speaker: Ms Maggie Lit	Ms Vienna Lam Tel: 2527 8898
7 THU 2:00 PM	**Zoom Lecture** **Updates on Menstrual Disorders Management - Hormonal Treatment and Myths - Online** Organiser:HKMA-KLN East Community Network Speaker: Dr. WONG Yin Yan, Ivy	Ms. Antonia Lee 2865 0943 1CME Point
7:00 PM	**Certificate Course on Renal Medicine 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong Society of Nephrology Speaker: Dr Wai-Yan LAU, Dr Ka-fai YIM	Ms Vienna Lam Tel: 2527 8898
12 TUE 7:00PM	**Certificate Course on Cardiology 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong College of Cardiology Speaker: Prof Cheung Man Yung	Ms Vienna Lam Tel: 2527 8898
13 WED 7:00PM	**Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, The Hong Kong Society of Professional Optometrists Speaker: Mr. Chan Ka Ho, Paco	Ms Vienna Lam Tel: 2527 8898
7:30 PM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting** Organiser: Hong Kong Neurosurgical Society Speaker: Dr SEE Ka Wing, Michael	Dr Calvin MAK Tel: 2595 6456
15 FRI 2:00 PM	**Zoom Lecture** **Update in Management of Lung Cancer - Online** Organiser: HKMA-Shatin Community Network Speaker: Dr. TONG, Macy	Ms. Candice Tong 2865 0943 1CME Point
18 MON 2:00 PM	**Zoom Lecture** **In Search Of Completely Clear Skin – Findings On PASI 100 Results From Clinical Trials And Real Life In Plaque Psoriasis - Online** Organiser:Hong Kong Medical Association Speaker: Dr. CHAN Yung	HKMA CME Dept. 2865 0943 1CME Point
19 TUE 7:00 PM	**Certificate Course on Cardiology 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong College of Cardiology Speaker: Dr Chan Kit	Ms Vienna Lam Tel: 2527 8898
20 WED 7:00 PM	**Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, The Hong Kong Society of Professional Optometrists Speaker: Miss Bibianna Yu	Ms Vienna Lam Tel: 2527 8898
21 THU 2:00 PM	**Zoom Lecture** **The Role of Novel Antidepressants in Managing Major Depressive Disorder (MDD) - Online** Organiser: HKMA-HK East Community Network Speaker: Dr. LAI Wing Him, Elvis	Ms. Candice Tong 2865 0943 1CME Point
7:00 PM	**FMSHK Executive Committee Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai , Hong Kong	Ms Nancy CHAN Tel: 25278898
8:00 PM	**FMSHK Council Meeting** Organiser: The Federation of Medical Societies of Hong Kong; Venue: Council Chamber, 4/F, Duke of Windsor Social Service Building, 15 Hennessy Road, Wanchai , Hong Kong	Ms Nancy CHAN Tel: 25278898
22 FRI 2:00 PM	**Zoom Lecture** **Nutrition Intervention for Type 2 Diabetes Mellitus (T2DM) Patients - Online** Organiser:HKMA-YTM Community Network Speaker: Dr. TSANG Man Wo	Ms. Candice Tong 2865 0943 1CME Point
26 TUE 7:00 PM	**Certificate Course on Cardiology 2021 (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, Hong Kong College of Cardiology Speaker: Dr Cheng Yue Hong	Ms Vienna Lam Tel: 2527 8898
27 WED 7:00 PM	**Certificate Course on Optometric Practice from Infants to the Elderly (Video Lectures)** Organiser: The Federation of Medical Societies of Hong Kong, The Hong Kong Society of Professional Optometrists Speaker: Dr Helen Eng OD	Ms Vienna Lam Tel: 2527 8898
28 THU 2:00 PM	**Zoom Lecture** **Breakthrough in Heart Failure Management: The Latest Scientific Update - Online** Organiser:HKMA-New Territories West Community Network Speaker: Dr. CHAN Leung Kwai, Jason	Ms. Antonia Lee 2865 0943 1CME Point

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20 October 2021	Amblyopia, Binocular Vision Anomalies and Vision Training	Miss Bibianna Yu BSc(Hons)Optom, MPhil, FAAO
27 October 2021	Vision Rehabilitation of Low Vision Patients	Dr. Helen Eng OD FAAO
3 November 2021	The Latest Clinical Studies on Myopia Management for Children	Dr. Ng Sheung Shun, Vincent BSc (Hons) Optom, Ph.D, FAAO
10 November 2021	Optometric Care on High Myopia	Dr. Ng Sheung Shun, Vincent BSc (Hons) Optom, Ph.D, FAAO
17 November 2021	Specialty Contact Lenses and Tips of Proper Contact lens Wear	Miss Yee Man Chi, Gigi MSc in Optometry, BSc (Hons) Optom, FBCLA

Date : 13, 20, 27 October & 3, 10, 17 November 2021 (Every Wednesday)
Duration of session: 1.5 hours (6 sessions)
Time : 7:00 pm – 8:30 pm
Course Feature: Video lectures (with Q&A platform for participants to post the questions)
Language Media : All lectures are conducted in Cantonese (except Lecture 3 is in English)
Quiz : Doctors and Optometrists are required to complete a quiz after the completion of each lecture
Course Fee : HK$1,000 (6 sessions)
Certificate : Awarded to participants with a minimum attendance of 70%
Deadline : 6 October 2021
Enquiry : The Secretariat of The Federation of Medical Societies of Hong Kong
Tel.: 2527 8898 Fax : 2865 0345 Email : vienna.lam@fmshk.org

CME and CNE Accreditation in application
9 CPD points for Optometrists for the whole course and the points will be awarded according to the number of hours attended
Online Application from website: http://www.fmshk.org

Answers to Radiology Quiz

Answers:

1. Left MCA infarct. MCA supplies the lateral aspect of frontal, temporal and parietal lobes, the corona radiata, globus pallidus, caudate and putamen. There will be contralateral hemiparesis and hemisensory loss of the face, upper and lower extremities. If the dominant side is affected, there would be aphasia due to the involvement of Broca's area, and Wernicke's area.

2. CT cerebral angiogram.

3. Hemorrhagic transformation.

4. Blurring of grey-white differentiation, dense MCA sign, cerebral oedema.

Dr Carol PY CHIEN
MBBS, FRCR

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References: 1. Search Drug Database, Department of Health website: http://www.drugoffice.gov.hk/eps/drug/productDetail/en/consumer/119712 as assessed 17 August 2020; 2. Acarizax® Package Insert Hong Kong Abbott Laboratories Ltd; June 2020

Acarizax Abbreviated Prescribing Information. Product name: ACARIZAX 12 SQ-HDM oral lyophilisate. Active ingredient: Standardised allergen extract from Dermatophagoides pteronyssinus and D. farinae. Indications: Diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) – adolescent and adult patients (12-65 years) with persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication; Adult patients (18-65 years) with house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Posology and method of administration: one oral lyophilisate (12 SQ-HDM) daily for 3 years with reference to International treatment guidelines. Sublingual route. The first oral lyophilizate should be taken under medical supervision, and patient should be monitored for at least half an hour. Contraindications: Hypersensitivity to Gelatine (fish source), mannitol, sodium hydroxide; Patients with FEV1 < 70% of predicted value (after adequate pharmacological treatment) at initiation of treatment; severe asthma exacerbation within the last 3 months; patients with asthma and concomitant acute respiratory tract infection; active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance; acute severe oral inflammation or oral wounds. Special warnings and precautions for use: Asthma exacerbation; Reduction in other asthma control medication; Severe systemic allergic reactions – recommendation for medical supervision at first oral lyophilisate intake; Oral inflammation; Local allergic reactions; Eosinophilic esophagitis; Autoimmune diseases in remission; Food allergy (trace of fish protein present). Interactions: Concomitant therapy with symptomatic anti-allergic drugs may increase the tolerance level of the patient to immunotherapy. Fertility, pregnancy and lactation: Acarizax treatment should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may be continued after medical evaluations. Effects on ability to drive and use machines: no or negligible influence. Undesirable effects: Very common: nasopharyngitis, ear pruritus, throat irritation, lip oedema, oedema mouth, oral pruritus; Common: bronchitis, pharyngitis, rhinitis, sinusitis, dysgeusia, asthma, dysphonia, dyspnoea, oropharyngeal pain, pharyngeal oedema, abdominal pain, diarrhea, nausea, oral discomfort, oral mucosal erythema, paraesthesia oral, stomatitis, tongue oedema, vomiting. Date of revision: Jun 2020

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References :

1. L. Pradelli et al. /Clinical Nutrition 33 (2014) 785-7 92
2. Singer et al. (2009) ESPEN Guidelines on parenteral nutrition: Intensive Care. Clinical Nutrition 28: 387-400
3. Braga et al. (2009) ESPEN Guidelines on Parenteral Nutrition: Surgery. Clinical Nutrition, 28: 378-386
4. Biesalski HK. Gastroenterology 2009;137(5):92-104
http://www.espen.org/espenguidelines.html

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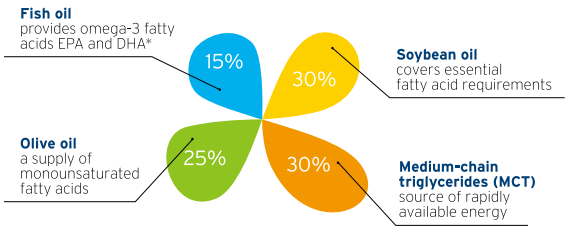

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