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What Should We Know About Anxiety Disorder?

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* In steady-state PK/PD analyses in T1DM, Toujeo* showed a more stable and prolonged glucose lowering **effect compared to insulin glargine 100 units/mL**.[1,8]

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References: 1. Toujeo® Hong Kong prescribing information. 2020 ver 1. 2. YkH-Järvinen H, et al. Diabetes Care. 2014:37:3235-3243. 3. Bolli GB, et al. Diabetes ObesMetab. 2015:17:386-394. 4. Terauchi Y, et al. Diabetes Obes Metab. 2016:18:366-374. 5. Home PD, et al. Diabetes Care. 2015:38:2217-2225. 6. Matsuhisa M. et alDiabetes Obes Metab. 2016:18:375-383. 7. Bergenstal RM, et al. Diabetes Care. 2017:40:554-560. 8. Becker RHA, et al. Diabetes Care 2015;38(4):637-43 9. Singh R, et al. Eur Endocrinol 2018;14:47-51 10. Pohlmeier H, et al. J Diabetes Sci Technol 2017;11;263-269

Abbreviated prescribing information: Presentation: Insulin glargine 300 IU/ml solution for injection. **Indications** Treatment of diabetes mellitus in adults, adolescents and children from the age of 6 years. **Dosage** Once daily (preferably at the same time every day up to 3 hours before or after the usual time of administration), with adjusted individual dosage. Please refer to the full prescribing information for guidelines on switching between other insulin preparations. **Administration** Subcutaneous injection. Toujeo is NOT INTENDED FOR INTRAVENOUS USE since it could result in severe hypoglycaemia. Toujeo must not be drawn from the cartridge of the SoloStar pre-filled pen into a syringe or severe overdose can result. **Contraindications** Hypersensitivity to insulin glargine or to any of the excipients. **Precautions** Toujeo has not been studied in children below 6 years of age. Elderly: progressive deterioration of renal function may lead to a steady decrease in insulin requirements. Renal impairment: insulin requirements may be diminished due to reduced insulin metabolism. Hepatic impairment: insulin requirement may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. Perform continuous rotation of injection site to reduce risk of lipodystrophy and cutaneous amyloidosis. Blood glucose monitoring is recommended after change in injection site. Hypoglycaemia. Intercurrent illness. Combination of Toujeo with pioglitazone. Medication errors prevention. **Interactions** Effects enhanced by oral antidiabetics, ACEI, disopyramide, fibrates, fluoxetine, MAOIs, pentoxifylline, propoxyphene, salicylates, sulfonamide antibiotics. Effects reduced by corticosteroids, danazol, diazoxide, diuretics, glucagons, isoniazid, oestrogens and progestogens, phenothiazine derivatives, somatropin, sympathomimetics, or thyroid hormones, atypical antipsychotics and protease inhibitors. Beta-blockers, clonidine, lithium or alcohol may either potentiate or weaken the effects of insulin. Pentamidine may cause hypoglycaemia, followed by hyperglycaemia. The signs of adrenergic counter-regulation may be reduced or absent under the influence of sympatholytic medicinal products such as Beta-blockers, clonidine, guanethidine and reserpine. **Fertility, pregnancy and lactation** Animal studies do not indicate direct harmful effects with respect to fertility and reproductive toxicity. The use of Toujeo may be considered during pregnancy if clinical needed. It is unknown whether insulin glargine is excreted in human milk. **Overdose** Insulin overdose may lead to severe and sometimes long-term and life-threatening hypoglycaemia. Mild episodes of hypoglycaemia can usually be treated with oral carbohydrates. More severe episodes with coma, seizure or neurologic impairment may be treated with glucagon (intramuscular or subcutaneous) or concentrated glucose solution (intravenous). **Undesirable effects** Hypoglycaemia, lipohypertrophy, injection site reactions. For common, uncommon, rare and very rare undesirable effects, please refer to the full prescribing information. **Storage:** Before first use: Store in a refrigerator (2°C - 8°C). Do not freeze. Protect from light. After first use: Store below 30°C. Use within 42 days. Do not freeze. **Preparation** Toujeo 5 x 1.5ml (450IU) pre-filled pens.
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Dear Reader,

Anxiety disorders are one of the most prevalent psychiatric disorders, and up to 30% of the population are reported to be affected by an anxiety disorder during their lifetime. The disease burden and economic costs of anxiety disorders are substantial, thus timely, effective treatments for controlling the disease are essential. Although effective therapies against anxiety disorders are available, early identification of patients with the disorder is still clinically challenging. In the current Feature Story, Dr. Chong King Yee was invited to share her experiences in managing anxiety disorders and discuss certain clinical issues related to psychiatric disorders.

The Focus section covered the threats of paediatric inflammatory bowel disease (pIBD), a chronic inflammatory disease of the gastrointestinal tract (GIT) characterised by the repetitive inflammation of the GIT caused by an abnormal immune response. As the disease manifests with a variety of intestinal and extraintestinal symptoms that can present insidiously or in a fulminant manner, diagnostic delay is common for pIBD. Notably, early antibiotic exposure would further increase the risk of pIBD. Fortunately, the development of biologic treatment offers new hope in the management of pIBD. Recent findings about the clinical performance of various biologics in countering pIBD were highlighted.

Besides the thematic topics, updates on the pharmacologic management of Parkinson's disease, and the benefits of vaccination in post-exposure prophylaxis of rabies and hand, foot and mouth disease were discussed in the Industry Updates. In particular, the strategies for eliminating hepatitis C (HCV) infection in marginalised communities were covered as well.

In the Epoch section, clinical data evaluating the effects of once-weekly subcutaneous semaglutide in non-treatment-seeking adults with alcohol use disorder (AUD) were presented. Also, the outcomes of managing acute myocardial infarction with SGLT2 inhibitor were reviewed. Essentially, the clinical implications of the newly published consensus on the management of lupus nephritis for the Asia-Pacific region were featured.

Hope you enjoy this issue!

Dr. Roy Yuen-chi Lau
PhD, DBA, MPH, MMedSc, MA, BSc, FRSPH, MIET, MRSC, MSB, CBiol, CSci, MRACI CChem
Editor-in-Chief

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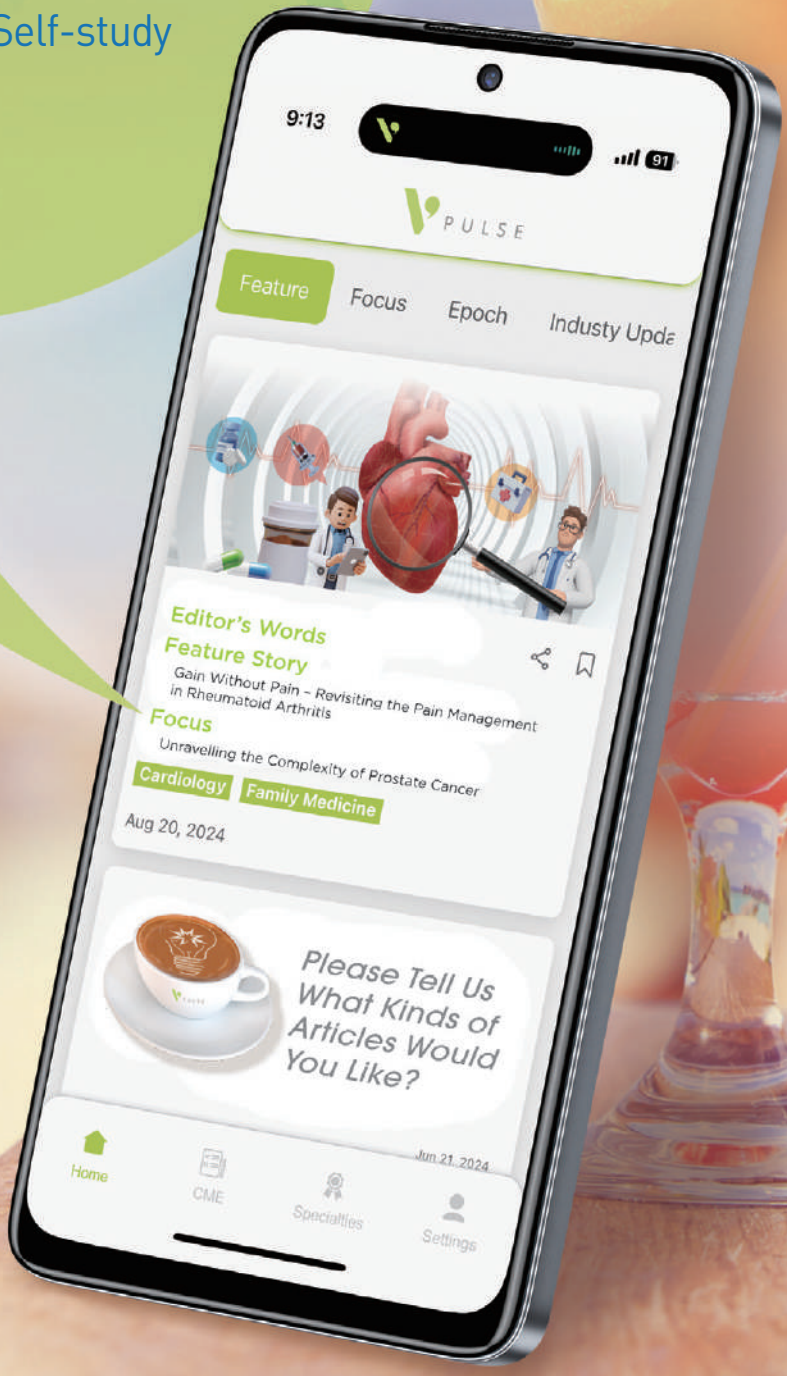

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by Dr. Roy Lau

What Should We Know About Anxiety Disorder?

Dr. Chong King Yee
Specialist in Psychiatry

Anxiety disorders are one of the most prevalent psychiatric disorders, up to 30% of the population are reported to be affected by an anxiety disorder during their lifetime. While anxiety disorders are associated with a significant disease burden and economic costs, substantial underdiagnosis and undertreatment of the disorders have been demonstrated in clinical settings[1]. In the current Feature Story, Dr. Chong King Yee was invited to share her experiences in managing anxiety disorders and discuss specific clinical issues in psychiatric disorders, including the feasibility of anxiety screening and the role of artificial intelligence (AI).

The Keys in Diagnosing Anxiety Disorders

Anxiety is a normal reaction to stress, and an appropriate level of anxiety is essential for us to face dangers. However, medical attention will be required when fears and anxieties are disproportionate to a threat, are severe and enduring, or disrupt normal functioning. In contrast to normal anxious feelings, the core features of anxiety disorders include excessive fear and anxiety or avoidance of perceived threats that are persistent and impairing. Anxiety disorders involve dysfunction in brain circuits that respond to danger[2].

There are various types of specific anxiety disorders sharing characteristics of excessive fear and worry along with somatic symptoms. Accordingly, Dr. Chong noted that generalised anxiety disorder (GAD), panic disorder (PD), specific phobia, obsessive-compulsive disorder (OCD), and mixed anxiety–depressive disorder (MADD) are anxiety disorders commonly observed in Hong Kong.

Regarding the assessment of patients reporting anxiety symptoms, Dr. Chong highlighted the importance of a comprehensive evaluation of the patient's medical history to appreciate if there are any physiological causes. Attention should also be paid to the duration and severity of symptoms. "While anxiety disorders adversely affect patients' daily life, including their study, career, and social life, their impacts in these aspects have to be evaluated as well." Dr. Chong emphasised.

Who Are at Greater Risk for Anxiety Disorders?

Dr. Chong outlined that people with a family history of mood disorders would have a higher risk of anxiety

disorders. Additionally, she noted that there are environmental factors contributing to the increased risk of anxiety disorders, such as a stressful working condition, tension among family members, and childhood adversity.

Of note, an analysis of a nationally representative sample of the adult population of the United States (U.S.) by Blanco *et al*. (2014) reported that low self-esteem, family history of depression, female sex, childhood sexual abuse, White race, years of education, number of traumatic experiences, and disturbed family environment increased the risk of anxiety disorders[3].

Interestingly, Dr. Chong addressed that there are emerging clinical data suggesting that inadequate sleep and overtime work are associated with an increased risk of anxiety disorders. In this regard, the analysis of German Health Survey data by Ramsawh *et al*. (2009) indicated that most anxiety disorders were significantly associated with reduced sleep quality, with the strongest associations observed in social phobia and GAD. Essentially, the study concluded that individuals with anxiety disorders and poor sleep experience significantly worse mental health-related quality of life (HRQOL) and increased disability relative to those with anxiety disorders alone[4].

Besides, a study of 7,786 Japanese workers by Ishida *et al*. (2020) demonstrated the association between overtime-working environment (OWE) and individual psychological distress that a 10% increase in the OWE was associated with a 16% higher risk of individual psychological distress (**Figure 1**)[5].

From the brief highlights above, the risk factors for anxiety disorders are highly diversified and can occur at different stages within a person's lifetime.

The Disease Burden of Anxiety Disorders

Anxiety disorders place a significant humanistic burden on affected individuals. Compared to non-anxious individuals, those with anxiety disorders are more likely to have reduced psychosocial functioning and life satisfaction. In addition, the socioeconomic burden of anxiety disorders is substantial.

Dr. Chong outlined that there are 3 major categories of anxiety symptoms. Firstly, most patients develop emotional symptoms, which are expressed as excessive fear, worry, and/or anxiety. Dr. Chong recommended that an investigation on the factors triggering anxiety would help in understanding the aetiology, though there can be no specific triggering factor for certain GAD cases.

Besides, patients with anxiety may exhibit cognitive symptoms such as catastrophic thoughts. Dr. Chong noted that these patients typically exaggerate the impacts of matters, no matter how minor and rare they are. "Many of them frequently say, "Oh my god, it's bad!" she described. The way they interpret issues is different from non-anxious people. For instance, if they travel by bus, they may worry if they will be killed in a traffic accident caught by the bus. Another common symptom is worry about suffering from diseases. These patients would undergo many medical tests due to extremely minor symptoms.

Moreover, patients with anxiety disorders can exhibit somatic symptoms, including increased heart rate, headache, nausea, vomiting, and other GI symptoms, upon minor triggering. Dr. Chong remarked that some cases of irritable bowel syndrome (IBS) are associated with anxiety disorders, whereas resolving anxiety leads to a relief of GI symptoms. Notably, a previous meta-analysis by Sibelli *et al*. (2016) confirmed that self-reported anxiety and depression provide a twofold risk for IBS onset[6].

Apart from physiological symptoms, anxiety disorders also significantly impact the socioeconomic status and overall well-being of the patients. Dr. Chong said

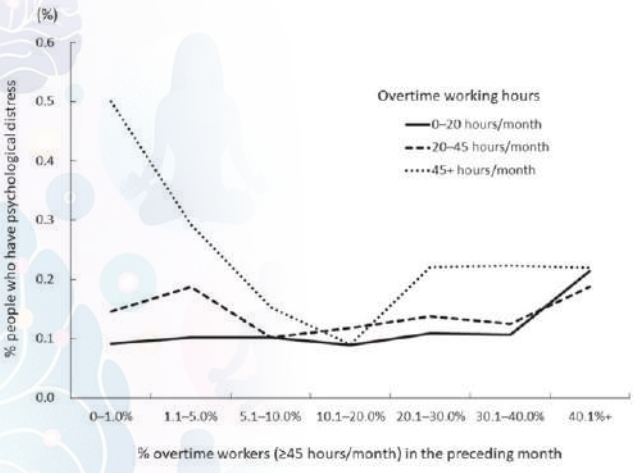

Figure 1. *The association between the percentage of overtime work and the percentage of workers with psychological distress*[5]

that some patients with anxiety disorders may have extremely high standards and expectations for all matters in daily life, not only for themselves but also for other people, such as colleagues, classmates, and family members. Attempting to meet such unrealistic standards would create stress for other people, thus leading to interpersonal conflicts.

Besides, patients with anxiety disorders may have difficulty coping with the stress associated with uncertainties in the working environment. Hence, they would reject career or learning opportunities in order to avoid potential uncertainties. Furthermore, anxiety symptoms potentially increase absenteeism. Dr. Chong addressed that some students with the disorder would refuse to attend classes since they cannot cope with the stress in class. On the other hand, anxiety-related somatic symptoms, such as fibromyalgia, affect the leisure life of patients since physical discomfort prevents them from engaging in physical exercises and social events.

Anxiety Screening – To Be or Not to Be?

Provided the high prevalence of anxiety disorders as well as the associated significant disease burden and economic costs, routine anxiety screening theoretically could increase the likelihood that patients receive timely treatment, hence potentially saving years of distress and reducing economic burden. Nonetheless, Dr. Chong commented that routine screening for anxiety and other mood disorders would be practically difficult. "Patients with mood disorders may not participate in screening. Those people who have screening result positive, may not accept any further psychiatric assessment, referral or treatment," she explained.

Dr. Chong's comments aligned with the findings of a recent meta-analysis of 59 clinical studies by O'Connor *et al*. (2023) that no clinical benefit in anxiety and depression outcomes, global quality of life, and functioning was yielded by anxiety screening programs[7]. Instead of screening, Dr. Chong suggested identifying anxiety disorder cases based on clinical assessment of symptoms with high index of suspicion. "If an anxious patient complains about persistent somatic symptoms, such as palpitations, insomnia, aches and pains, gastrointestinal (GI) problems, referral to mental health professionals is recommended if symptoms persist despite usual treatment," she advised.

Opinions on the Clinical Management of Anxiety Disorders

Although timely identification of patients with anxiety disorders by screening may not be feasible, effective treatments for the disorders do exist. These treatments can be classified into pharmacotherapy and psychotherapy. Given anxiety disorders are related to the imbalance of various neurotransmitters in the brain, primarily norepinephrine, serotonin, and dopamine, most medications against anxiety disorders act by regulating the secretion and function of these neurotransmitters[8]. Remarkably, Dr. Chong noted that tranquillisers are commonly prescribed for insomnia. However, she emphasised that normal sleeping pattern will resume when anxiety symptoms improve. Thus, long-term use of tranquilliser is usually not required.

In managing anxiety disorders, Dr. Chong reminded that the symptoms exhibited by each patient are specific. Therefore, pharmacotherapy should be tailored for each patient, considering symptoms and side effect profiles. She mentioned that different patients may respond to the same medication differently. "The medication that works well in this patient may not be tolerated by the other patients," per Dr. Chong. Given there are many treatment options currently available for the long-term control of anxiety disorders, switching treatment can be considered if necessary.

Evidence-based psychotherapies, as pharmacotherapies, are considered first-line treatments for anxiety disorders. Psychotherapies range from low-intensity interventions incorporating self-help approaches, such as bibliotherapy, to high-intensity therapies with a specialised therapist according to disorder severity[2], whereas cognitive behavioural therapy (CBT) is the most frequently applied psychotherapy.

CBT is a short-term therapy derived from principles of behavioural and cognitive psychology. A key CBT component for most forms of anxiety disorder involves exposure to the feared stimuli, either in vivo or imaginal[2]. Practically, Dr. Chong outlined that CBT involves communication with the patients to figure out if there are any cognitive distortions triggering anxiety and providing guidance on coping with stress.

In particular, Dr. Chong introduced the application of mindfulness training in anxiety disorders, which teaches patients meditation techniques that increase awareness of present-moment experiences, including thoughts, emotions, and bodily sensations, with a gentle and accepting attitude towards oneself. In the randomised controlled trial (RCT) involving 93 patients with GAD by Hoge *et al*. (2013), 8-week mindfulness training was shown to reduce anxiety symptoms significantly and was associated with a greater increase in positive self-statements[9].

Regarding the choice of behavioural strategies in psychotherapy, Dr. Chong emphasised that we need to select the appropriate option according to the patient's interests, lifestyle, and personal needs.

The Under-diagnosed and Under-treated Disease

Even though numerous clinical data advocating the benefits of pharmacotherapy and psychotherapy, under-diagnosis and under-treatment are clinical challenges in managing patients with anxiety disorders, resulting in a low remission rate. Dr. Chong stated that some patients would deny suffering from anxiety symptoms and refuse to seek help from healthcare professionals, whereas others may not be aware the symptoms are related to anxiety. Thus, Dr. Chong highlighted the importance of detailed explanation for somatic symptoms so as to enhance patient's understanding.

Once anxiety disorder is diagnosed, ensuring patient adherence to treatment is the next challenge. Of note, the long duration of treatment effect onset would discourage patients. Dr. Chong opined that pharmacotherapies for anxiety disorders may take several weeks to generate noticeable benefits. Accordingly, patients may consider the treatment ineffective and not comply with it. Even worse, they might lose their trust towards physicians and give up treatment. Therefore, thorough communication with patients before treatment on the expected progress is essential for managing their expectations and enhancing their compliance.

Even if the treatment is effective, Dr. Chong said some patients would discontinue treatment due to misunderstanding about the treatment endpoint. "Patients might reduce or even discontinue treatment upon symptom improvement," she addressed. Essentially, Dr. Chong highlighted symptom improvement does not necessarily indicate a treatment endpoint. She emphasised that treatment completion should be considered as the state in which all symptoms are eliminated, and the patient's overall condition becomes comparable to that before the disease.

Prospectives in Anxiety Disorder Management

In recent years, notable progress has been made in developing and utilising AI-based applications and environments to improve the precision and sensitivity of diagnosis and treatment in various medical specialties. In psychiatry, there are investigations applying AI in preliminary assessment and identifying patterns that may suggest symptoms of anxiety, depression, or other mental health issues, analysing patient's speech for mood and stress assessment, behavioural coaching, etc[10].

Nonetheless, Dr. Chong commented that solid evidence supporting the use of AI in psychiatry is still limited. She remarked that anxiety often originated from uncertainty and perceived lack of support. Instead of using AI, having emotional support from family and friends, as well as the caring attitude of healthcare professionals, are essential for relieving anxiety.

Apart from advanced technology, Dr. Chong highlighted the importance of continuous professional development among healthcare professionals. The awareness of the linkage between the brain and other organs needs to be enhanced, especially in handling difficult-to-treat cases with unclear aetiologies. Interdisciplinary communication and continuous medical education (CME) are helpful means of maintaining up-to-date medical knowledge.

To conclude, Dr. Chong opined that psychiatric disorders are curable with good compliance with treatment. As the symptoms and responses to treatments are unique for each individual, patients should have their doctor well informed about their condition. "Promising treatment outcomes rely on the collaboration between patients and healthcare professionals", she expressed.

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Self Study Questions (1 CME point):

1. According to Dr. Chong, which of the following is/are anxiety disorders commonly observed in Hong Kong?

i. Generalised Anxiety Disorder
ii. Panic Disorder
iii. Mixed Anxiety Depressive Disorder

A) i only
B) i and ii
C) ii and iii
D) All of above

2. Based on the study by Blanco *et al*. (2014), which of the following factors increased the risk of anxiety disorders?

i. Family history of depression
ii. Being male
iii. Childhood sexual abuse

A) i only
B) i and ii
C) i and iii
D) All of above

3. Which of the following is a potential somatic symptom exhibited by patients with anxiety disorders?

A) Decreased heart rate
B) Delusion
C) Irritable bowel syndrome
D) Catastrophic thoughts

4. Which of the following statements is true?

A) Routine screening for anxiety and other mood disorders is practically helpful in ensuring timely treatment.
B) The systematic review by O'Connor *et al.* (2023) showed clinical benefit in anxiety and depression outcomes by anxiety screening programs.
C) Anxiety disorder can be identified through clinical assessment
D) None of above.

5. According to the article, which of the following about clinical management of anxiety disorders is/are correct?

i Long-term use of tranquillisers is usually not required
ii. CBT for most forms of anxiety disorders involves exposure to the feared stimuli
iii. Mindfulness training was shown to reduce anxiety symptoms significantly and was associated with a greater increase in positive self-statements

A) i only
B) i and ii
C) i and iii
D) All of above

This CME article was prepared by Dr. Chong King Yee and accredited by the Hong Kong Doctors Union (HKDU).

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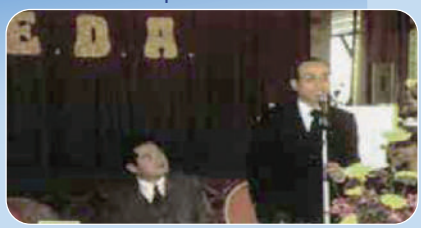

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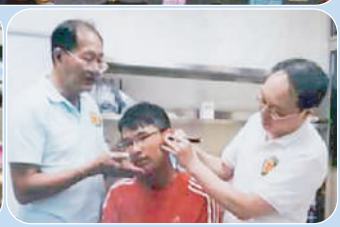

The liaison body between medical doctors and government departments

Member activities

by Dr. Mohsin Roshan

Improving Quality of Life in Parkinson's Disease: Safinamide's Impact beyond Motor Symptoms

Dr. Fung Bun Hey
Specialist in Neurology
Honorary Clinical Associate Professor, Department of Medicine & Therapeutics, Chinese University of Hong Kong (CUHK)

Case Presentation

A 72-year-old man, previously diagnosed with Parkinson's disease (PD) 10 years ago, presented with persistent end-of-dose resting tremor despite regular follow-up at a public hospital. He was partially dependent in his activities of daily living (ADL) and consulted Dr. Fung's clinic due to insomnia and ongoing PD-related symptoms.

Clinical examination and investigations

On examination, the patient exhibited a mild resting tremor in the right hand, rigidity and bradykinesia on the right side, truncal dykinesia, as well as a mildly festinated gait.

Treatment and outcome

The patient was initially treated with levodopa 250 mg/carbidopa 25 mg, 5 times a day and ropinirole 6 mg once daily. However, he reported only marginal improvements with his tremor and continued to experience "OFF" episodes with sialorrhea and jaw tremor. Moreover, his sleep disturbance has been exacerbated by nocturia and rhinorrhoea despite the use of hypnotics including zolpidem and lemborexant.

Subsequently, Dr. Fung initiated treatment with safinamide 50 mg once daily which led to a reduction in end-of-dose tremor. While reducing the levodopa dose, the safinamide dose was gradually uptitrated to 50 mg twice daily, resulting in no sudden "OFF" symptoms and less dyskinesia. More importantly, patient's quality of sleep also improved. Switching antihistamines further helped alleviate symptoms of the rhinorrhoea.

Overall, after the addition of safinamide for 4 months, there was a significant improvement in Parkinsonian symptoms, reduced sleep disturbances, and increased independent walking in this patient, and Dr. Fung commented that these could be attributed to the unique dopaminergic and glutamatergic modulation by safinamide.

Conclusion

Safinamide is an effective add-on therapy for PD patients experiencing wearing off, addressing both motor and non-motor symptoms, including sleep disturbance.

Safinamide 50 mg twice daily resulted in no sudden 'OFF' symptoms and less dyskinesia

Safinamide Improves Sleep and Daytime Sleepiness in Parkinson's Disease: Results from the SAFINONMOTOR Study[1]

Introduction

Safinamide is a third-generation reversible monoamine oxidase-B inhibitor with additional activity on the glutamatergic pathway[1]. A prospective, open-label, single-arm study conducted in 5 centres in Spain evaluated the effectiveness of safinamide on sleep and daytime sleepiness in 50 PD patients with a mean age of 68.5 years. At 6 months, 44 patients completed the follow-up and most patients initially on safinamide 50 mg/day were switched to 100 mg/day by Month 3 (±15 days). The outcomes were measured using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) scores at baseline and after Month 6 (±1 months)[1].

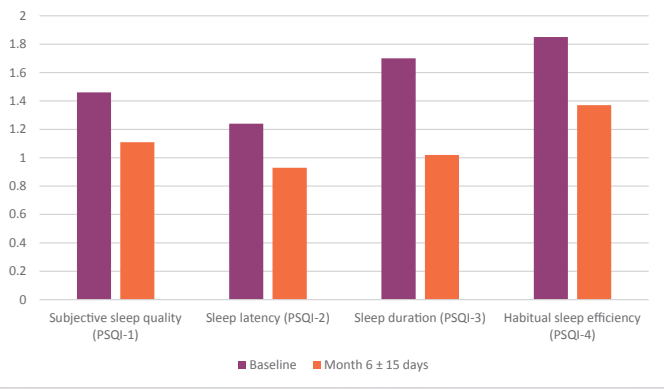

Figure 1: *Mean score of individual PSQI score domains at baseline and after 6 months[2]. Note: PSQI-component 5-7 (step disturbances, use of sleeping medication and daytime dysfunction) are not included due to insignificant results[1].*

Results

After 6 months of safinamide, the overall PSQI score reduced by 19.8% (from 10.43 ± 4.02 at baseline to 8.36 ± 4.41 at 6 months; $p = 0.001$). By domains, significant improvement were observed in PSQI-component 1-4 (PSQI-1 [subjective sleep quality] -23.9%, $p = 0.009$; PSQI-2 [sleep latency] -25.0%, $p = 0.025$; PSQI-3 [sleep duration] -40.0%, $p = 0.01$; and PSQI-4 [habitual sleep efficiency] -25.9%, $p = 0.023$) (**Figure 1**). Moreover, a significant reduction (−24.7%) in the ESS total score was observed[1].

Similarly, a retrospective study at a University Hospital's Movement Disorders Unit analysed the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms-Urinary subscale (SCOPA-AUT-U) in nondemented PD patients on safinamide 100 mg or other treatment regimens, and safinamide 100 mg was found to improve the total SCOPA-AUT-U as well as urgency, incontinence, frequency and nocturia subscale[2].

Conclusion

Safinamide at 100 mg shows a promising effect by enhancing sleep and reducing daytime sleepiness among PD patients[2], potentially by addressing urinary symptoms.

Safinamide 100 mg improved symptoms of urgency, incontinence, frequency and nocturia

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by Dr. Roy Lau

Advancing HCV Elimination in Marginalised Communities: Strategies and Challenges

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The availability of safe and effective oral direct-acting antivirals (DAAs) has paved the path to eliminating hepatitis C (HCV) infection. Accordingly, the World Health Organisation (WHO) addressed a global target in 2016 for the elimination of HCV as a public health threat by 2030. However, only an estimated 21% of the global population with chronic HCV had been diagnosed, and only 62% of them were treated by the end of 2019[1]. The identification of undiagnosed cases of HCV and subsequent treatment is additionally hindered by the fact that HCV is prevalent in socioeconomically deprived and marginalised groups, such as people who inject drugs (PWID)[2]. In the 37th Annual Scientific Meeting of the Hong Kong Association for the Study of Liver Diseases (HKASLD), Prof. Thomas Reiberger discussed the barriers towards HCV elimination in marginalised communities and outlined effective strategies to overcome barriers to an effective cascade of care towards HCV cure.

HCV – An Uncommon but Solid Public Health Issue

According to the Thematic Report on Viral Hepatitis 2020-2022, the overall prevalence of viraemic HCV infection in Hong Kong was 0.26% among local persons aged 15 to 84, and the prevalence was similar between females (0.43%) and males (0.20%). Of note, among persons who tested positive for HCV RNA (HCV-RNA+), 59.2% were infected by HCV genotype 1b representing the most common HCV genotype, whereas 19.9% were infected by HCV genotype 2, and 20.9% were infected by HCV genotype 6[3].

Prof. Reiberger commented that the local HCV prevalence was different from that of Europe. For instance, Thomadakis *et al*. (2024) recently reported that the chronic HCV prevalence in 29 of 30 European Union (EU)/European Economic Area (EEA) countries in 2019 was 0.50%, with the highest prevalence observed in eastern EU/EEA (0.88%). Essentially, the report highlighted that at least 35.76% of the overall chronic HCV prevalence in EU/EEA countries was associated with injecting drugs[4].

A Closer Look into the Marginalised HCV Communities

As per Prof. Reiberger, PWID, people living with HIV (PLHV), and people who are incarcerated[5] represent the marginalised populations at the greatest risk of HCV infection. He noted that the high HCV prevalence among PWID is mostly attributed to needle sharing. The shared transmission routes of HIV and HCV increase the risk for these co-infections. Besides, over-representation of PWID, lack of systematic screening programs, and limited access to care and treatment were found to be main reasons for the high HCV prevalence in prisons[6].

Focusing on the scenario of PWID, an HCV seroprevalence study conducted in local methadone clinics by Lee *et al*. (2006) reported an 85% prevalence rate of anti-HCV seropositivity in this community[7].

Additionally, another study by Wong *et al*. (2013) involving PWID recruited at their gathering places indicated an anti-HCV prevalence of 81.7%[8]. Apart from the current PWID, a local study involving 365 ex-PWID revealed that 73.4% of the participants were HCV-positive[9]. Hence, the findings highlighted the urgent need for effective strategies to reduce HCV prevalence in marginalised communities.

Main Barriers towards HCV Elimination in Marginalised Communities

The incidence of hepatitis C can be dramatically reduced by using DAAs for persons recently infected with HCV. Prof. Reiberger noted that the spontaneous clearance (SC) rate of recently acquired HCV is low, and most cases become chronic. As demonstrated in the PROBE-C study by Monin *et al*. (2023), which included 464 HIV-positive persons recently infected with HCV, only 11.9% achieved SC, while the remaining cases had progressed to chronic infection with persistent viremia of HCV. Importantly, 18.3% and 16.4% of cases, respectively, had not received antiviral treatment and did not achieve sustained virologic response (SVR) despite treatment (**Figure 1**)[10]. Prof. Reiberger stressed that a delay in clearing HCV, i.e. resulting on ongoing viremia would pose an ongoing transmission risk for HCV transmission.

Prof. Reiberger outlined that providing HCV care to the marginalised cohorts is practically difficult due to stigmatisation, unstable housing, and mistrust of the healthcare system[5]. Remarkably, many individuals are unaware of their HCV infection status and have limited access to healthcare services. Moreover, poverty and high out-of-pocket costs for treatment also hinder treatment for the marginalised HCV communities.

Besides patient-related factors, Prof. Reiberger noted that inadequate national policies, lack of integrated care systems, and restrictive treatment guidelines are additional barriers to HCV treatment.

Efficacious Therapy for Eliminating HCV

Prof. Reiberger emphasised that DAAs are highly effective and can cure hepatitis C in literally all patients. "If a patient remains compliant with intake of the antiviral medication, they will be cured from HCV", he said. The recent SVR10K study by Aleman *et al*. (2024) provided real-world evidence on the efficacy of 12-week DAA treatment with sofosbuvir/velpatasvir (SOF/VEL) without ribavirin (RBV) across 10 study sites globally, accounting for >6,000 HCV patients. The results indicated that among the effectiveness population (n=6,095), >98% of the patients showed SVR outcomes, regardless of sex (99.0% in females vs 98.7% in males) and age (under 50 years: 99% vs above 50 years: 98%)[11]. The results thus confirmed the pan-geographic efficacy across age and gender of SOF/VEL in real-world settings.

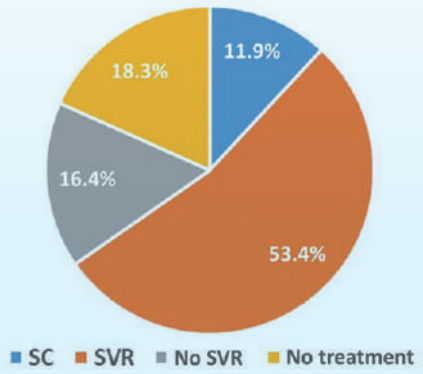

Figure 1: *Virologic outcomes in PROBE-C study*[10]

While SOF/VEL effectively suppresses HCV viral load, the treatment outcomes may be affected by patient adherence. Accordingly, the SIMPLIFY study by Cunningham *et al*. (2018) investigated treatment adherence to 12 weeks of once-daily SOF/VEL treatment among HCV-infected people with recent injecting drug use. Among the participants who completed treatment (n=100), 32% were considered non-adherent (<90% adherence). Interestingly, the results reflected that the SVR was still similar among adherent and non-adherent populations (94% vs 94%, p=0.944)[12].

Besides, a prospective, multi-centre pragmatic trial of community-based SOF/VEL therapy involving 755 HCV-infected people who use drugs (PWUD) by Litwin *et al*. (2022) indicated that 85% of participants achieved SVR at week 12 (SVR12) with at least 35 doses over the 12-week treatment course, whereas 65% of participants achieved SVR12 with <21 doses of SOF/VEL (**Figure 2**)[13]. Therefore, the result suggested that a high proportion of participants receiving SOF/VEL achieved SVR though the adherence was suboptimal.

Simplified HCV Management with Minimal Monitoring Strategy

In addition to using effective therapy, Prof. Reiberger highlighted the implication of a simplified HCV management approach, the Minimal Monitoring (MinMon) Strategy. "It (MinMon strategy) may be useful to cut the unnecessary steps, while genotyping is easily be crossed out since we have SOF/VEL, which requires no pre-treatment genotyping and its dosing is simple," he commented. The MinMon strategy is particularly useful in settings with limited resources.

Prof. Reiberger outlined that the MinMon strategy was characterised by 4 components: (i) no pre-treatment genotyping, (ii) dispensing full treatment, i.e. all 84 SOF/VEL tablets at initiation, (iii) no scheduled face-to-face visits or laboratory monitoring during treatment and (iv) remote contacts at week 4 for adherence and week 12 for SVR scheduling. The outcome of the MinMon strategy in managing HCV was confirmed in the phase-4 MINMON trial by Solomon *et al*. (2022) that 89% of the 397 patients reported taking 100% of the SOF/VEL treatment during the 12-week course, and 95% of the patients who initiated treatment achieved SVR[14]. Hence, the MinMon strategy with SOF/VEL regimen effectively reduces the burden on the healthcare system without compromising patient compliance and efficacy to cure HCV.

The Keys to Eliminate HCV in Marginalised Communities

Retaining persons in marginalised communities to HCV care is challenging and thus, patient adherence to antiviral treatment may be suboptimal. Undoubtedly, health education and social support by government and non-government organisations (NGOs) are crucial to improving awareness of HCV and its potential consequences and promoting diagnosis and treatment rate. According to Prof. Reiberger, effective therapy and a simplified HCV management approach are essential to optimise treatment outcomes. In this regard, the MinMon strategy with SOF/VEL treatment has been demonstrated to be an effective strategy for eliminating HCV.

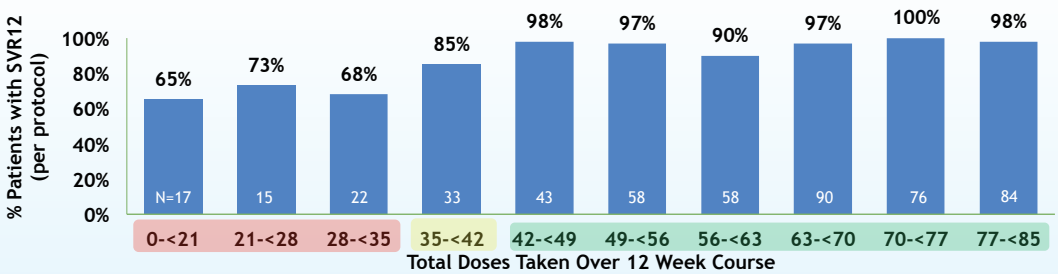

Figure 2: *SVR12 rate by total SOF/VEL doses taken over 12 Weeks*[13]

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Abbreviated Prescribing Information (EU-DEC20-HK-MAR21)
ADCETRIS 50 mg powder for concentrate for solution for infusion.
Active Ingredient: Brentuximab vedotin Indication: Treatment for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD); Treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; Treatment for relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT) or at least 2 prior therapies when ASCT or multi-agent chemotherapy is not a treatment option; In combination with cyclophosphamide, doxorubicin and prednisone (CHP) for the treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL); relapsed or refractory sALCL; Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy. Dose & Administration: Previously untreated HL: In combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]), 1.2mg/kg IV infusion over 30 min on days 1 and 15 of each 28-day cycle for 6 cycles. HL at increased risk of relapse or progression following ASCT & CTCL after at least 1 prior systemic therapy: 1.8 mg/kg IV infusion over 30 min every 3 wk up to max of 16 cycles. Previously untreated sALCL: In combination with chemotherapy (cyclophosphamide [C], doxorubicin [H] and prednisone [P] [CHP]), 1.8 mg/kg IV infusion over 30 minutes every 3 weeks for 6 to 8 cycles. Relapsed or refractory HL & relapsed or refractory sALCL: 1.8 mg/kg IV infusion over 30 min every 3 wk, patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a max of 16 cycles. Contraindications: Hypersensitivity to brentuximab. Combined use of brentuximab & bleomycin. Pregnancy & lactation. Special Population: Closely monitor for new or worsening neurological, cognitive or behavioural signs or symptoms suggestive of progressive multifocal leukoencephalopathy (PML); new or worsening abdominal pain suggestive of acute pancreatitis; new or worsening pulmonary symptoms; emergence of serious & opportunistic infections; immediate & delayed infusion-related reactions. Discontinue use if anaphylaxis & Stevens-Johnson syndrome occurs. Patient w/rapidly proliferating tumour & high tumour burden at risk of tumour lysis syndrome. Monitor for symptoms of neuropathy, Patient experiencing new or worsening peripheral neuropathy may require delay & dose reduction or discontinuation of treatment. Monitor CBC prior to therapy; serum glucose. Patient w/ an elevated BMI w/ or w/o history of DM; renal & hepatic impairment; on controlled Na-diet. Women of childbearing potential should use 2 methods of contraception during & until 30 days after therapy. Men should not father a child during therapy & for up to 6 mth after last dose. May affect ability to drive or operate machinery. Childn & elderly. Adverse Reactions: Infection, sepsis/septic shock, upper resp tract infection, herpes zoster, pneumonia, neutropenia, anaemia, thrombocytopenia, hyperglycaemia, peripheral sensory neuropathy, peripheral motor neuropathy, dizziness, demyelinating polyneuropathy, cough, dyspnoea, diarrhoea, nausea, vomiting, constipation, elevation of ALT/AST, alopecia, pruritus, rash, myalgia, arthralgia, back pain, fatigue, pyrexia, infusion-related reactions & chills.

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C-APROM/HK/ ADCE/003 (03/2022)

by Dr. Feng Xue

Innovative Post-Exposure Prophylaxis Treatment of Rabies by Monoclonal Antibody Cocktail

Dr. Beatriz P. Quiambao

- *Former President of Pediatric Infectious Disease Society of the Philippines*
- *Former Officer-in-Charge of the Assistant Director's Office and the Chief, Clinical Research Division of the Research Institute for Tropical Medicine (RITM), Philippines*
- *Member of World Health Organization (WHO) Expert Panel on Rabies and the Asian Rabies Advisory Group of Experts*

Rabies is a zoonotic disease caused by an RNA virus from the family Rhabdoviridae, genus Lyssavirus.[1] Currently, rabies is prevalent in over 100 countries and regions worldwide.[2] When rabies virus reaches the brain, the damage causes neurological symptoms.[3] Once symptoms appear, rabies is almost 100% fatal.[4] Rabies immunoglobulins (RIG) are presently used as post-exposure prophylaxis (PEP) for those exposed to the virus. However, due to certain concerns (such as cost, safety, and availability) for both human RIGs (HRIG) and equine RIGs (ERIG), a new treatment approach using a combination of two humanized monoclonal antibodies (mAb) has been proposed to offer better protection against various rabies virus (RABV) strains.[5-8] To enhance the understanding of the current knowledge in this field, on December 13, 2024, the 11th Asian Congress of Pediatric Infectious Disease in Hong Kong invited Dr. Beatriz P. Quiambao, a renowned pediatric infectious disease specialist from the Philippines, to discuss issues on rabies PEP, and present SYN023, the world's first humanized mAb cocktail for rabies.[9*]

Introduction

Dr. Quiambao started her presentation with the epidemiology of rabies. RABV belongs to a group of viruses referred to as lyssaviruses.[1] More than 99% of human rabies cases are transmitted via dogs.[1] Although canine rabies can be eliminated with the necessary tools in place for the control and elimination rabies remains a serious public health problem in more than 100 countries and territories, mainly in poor and rural areas of Asia and Africa.[1,2,10,11] RABV can spend days to weeks in the body before it invades the nervous system.[3] Once clinical symptoms appear, rabies is virtually 100% fatal.[4] Rabies deaths are preventable with timely PEP which prevents the virus from reaching the central nervous system. PEP consists of extensive wound washing; a course of human rabies vaccine; and, if indicated, administration of RIGs (**Figure 1**).[10]

Monoclonal Antibody Cocktails Against Rabies

Dr. Quiambao opined that although RIGs are currently used as a PEP measure for individuals exposed to RABV, concerns are raised regarding their cost, safety, and availability. Both HRIG and ERIG pose a

risk of transmitting bloodborne pathogens; and ERIG additionally carries a risk for severe allergic reactions. Despite HRIG being the preferred choice for PEP, it is expensive and often in short supply.[5,6] These have led to WHO recommendations for using anti-RABV mAbs as an alternative treatment (**Figure 1**).[7,10] Dr. Quiambao stressed that the WHO has put forward a recommendation that if mAbs are being considered for the prevention of rabies, then at a minimum, two mAbs targeting different antigenic sites of the glycoprotein should be included in the use of antibody cocktails.[7,8] She then introduced to the audience SYN023, an antibody cocktail which is a mixture of two humanized mAbs, zamerovimab and mazorelvimab, that bind to non-overlapping epitopes on the RABV glycoprotein.[12] The humanized mAbs are an ideal alternative to RIG since they are more affordable, safe, and can be produced on a large scale with standardized quality.[13,14] SYN023 has been reported to neutralize a wide spectrum of RABV strains, covering 67 strains around the globe with 100% neutralization.[8,15]

Syn023-004: Phase 2B Study on Syn023

To evaluate the effectiveness and safety of SYN023, Dr. Quiambao led SYN023-004, a phase 2b randomized controlled trial, in which 448 patients in two risk substrata of WHO Category III exposure (Low Risk and Normal Risk Groups^) were randomly allocated to receive either 0.3 mg/kg SYN023 or 0.133 mL/kg HRIG, injected in and around the wound site(s), plus a course of rabies vaccination. Patients were followed for safety and absence of rabies for ≥1 year.[12]

Dr. Quiambao then shared effectiveness findings of SY023-004. Regarding the primary efficacy endpoints[§], the geometric mean titer (GMT) of serum rabies virus neutralizing activity (RVNA) for the SYN023 group was superior to the HRIG group on Study Day 8 for both the low risk (SYN023 to HRIG ratio 29.64; 97.5 % confidence interval [CI]: 19.39, infinity) and normal risk groups (19.42; 97.5 % CI: 16.10, infinity) with $P < 0.0001$. On Day 99, the RVNA response rate, which is the proportion of subjects with RVNA serum concentration ≥ 0.5 IU/mL, showed non-inferiority of SYN023 in maintaining protective RVNA levels. No probable or confirmed rabies cases occurred in any of the study groups.[12]

Secondary endpoint[¶] analyses showed that the GMT of RVNA was higher with SYN023 throughout the 2-week post-treatment period and was similar through Day 99. Remarkably, in the Normal Risk Group, 99.4% of SYN023 recipients (n = 154) had protective RVNA levels on Day 4 compared to only 4.5% of HRIG recipients (n = 156). On Day 8, 98.1 % SYN023 versus 12.2 % HRIG recipients were protected. The proportion of subjects with RVNA serum concentration ≥0.5 IU/mL was higher in the SYN023 group than HRIG through Day 15, and was similar through Day 99. A greater $AUEC_{1\text{-}15}$ [#] was observed in SYN023 recipients.[12]

Regarding safety, Dr. Quiambao stated that SYN023 has an adverse event (AE) profile that is acceptable and manageable. Overall, the incidence rate of unsolicited treatment-emergent adverse events (TEAE) was similar in both treatment groups. The majority of solicited TEAEs were mild or moderate; and there was no

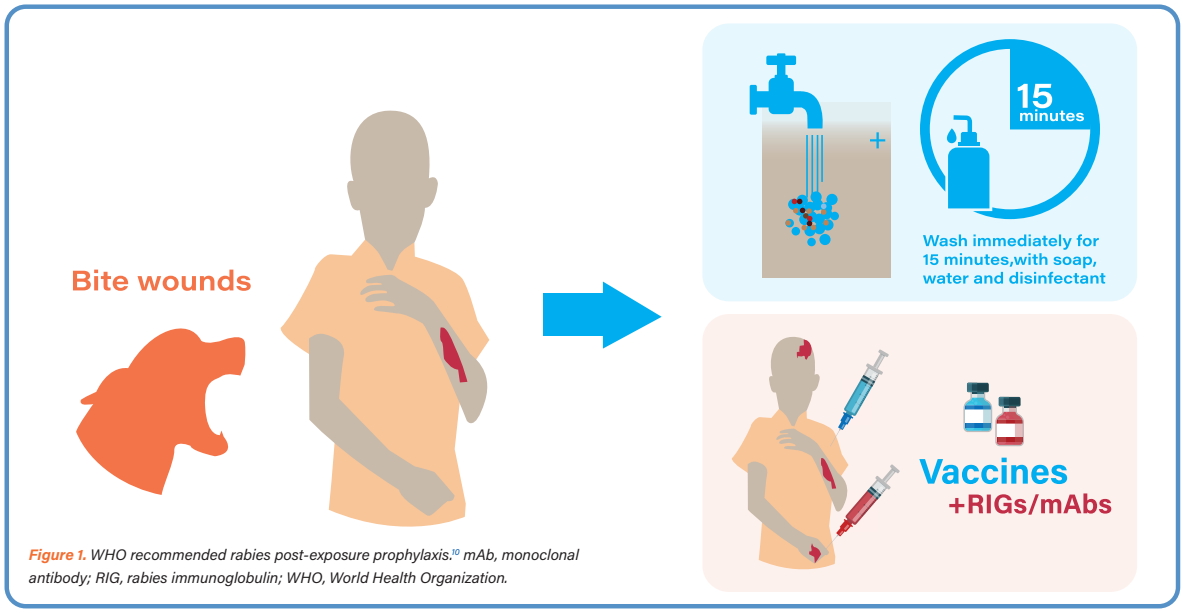

Figure 1. WHO recommended rabies post-exposure prophylaxis.[10] mAb, monoclonal antibody; RIG, rabies immunoglobulin; WHO, World Health Organization.

severe or very severe solicited TEAE. Additionally, there were no clinically significant changes in hematology, clinica chemistry, coagulation, vital signs, or physical examinations.[12]

In conclusion, rabies is a deadly infectious disease that targets mainly the central nervous system. SYN023 has been shown to act rapidly and provide a significantly higher RVNA level than HRIG shortly after exposure to rabies, a protection that is most needed especially in case of WHO Category III exposures. Although the RVNA concentrations decreased from Day 15 onwards, the observed levels of RVNA were not inferior to HRIG recipients. SYN023 also has a favorable safety profile. Thus, SYN023 represents itself as a potential effective and safe replacement for RIG against rabies virus.

* *SYN023 has obtained approval by the National Medical Products Administration of mainland China in 2024; but has not been registered in Hong Kong.*[9]

^ *The Low Risk Group included bites to the foot, ankle, leg, or trunk; licks to broken skin; scratches with or to broken skin; unprotected bat exposure; or mucous membrane contamination by saliva or neural tissue. Bites to the head, neck, or genitalia were excluded from the initial and general enrollment. The Normal Risk Group included all exposures as per WHO Category 3 exposure, including bites to the head/neck, genitalia, arms and hands.*[12]

§ *The 4-part composite primary efficacy objective included the following elements: (1) to demonstrate that the Day 8 post-administration GMT of RVNA was superior in SYN023 recipients compared to HRIG recipients, (2) to demonstrate that the Day 99 GMT of RVNA was not inferior in SYN023 recipients compared to HRIG recipients, (3) to demonstrate that the Day 99 RVNA response rate (i.e. the percentage of patients with RVNA concentration ≥ 0.5 IU/mL) was not inferior in SYN023 recipients compared to HRIG recipients, and (4) to show absence of rabies infection in any SYN023 recipient through 365 days of post-administration follow-up.*[12]

¶ *Secondary objectives were to evaluate safety in each treatment arm, to demonstrate superiority of RVNA-based endpoints with SYN023 at additional time points (Day 4, Days 1–15), to describe RVNA response rates and GMT of RVNA ratios over the study period, to evaluate any impact of body mass index on RVNA in SYN023 recipients, and to assess incidence and effects of anti-drug antibodies.*[12]

 # Area under effective curve from Day 1 to 15.[12]

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FORXIGA - your choice of SGLT2i with mortality benefits in CKM management[1*]

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Forxiga reduces kidney function decline, ESKD, and renal or CV death

39% RRR[2]

vs placebo
(HR 0.61 (95% CI:0.51, 0.72); P<0.001; N=4304)

Heart failure:

Forxiga reduces time to the first occurrence of hospital admission for worsening HF or death from CV causes **across the range of EF**[3]

22% RRR[3]

vs placebo
(HR 0.78 (95% CI 0.72–0.86); P < 0.001)

T2D:

Xigduo XR provides powerful glycaemic control in **once daily combination**

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HbA1C from baseline

*Forxiga (dapagliflozin) is indicated for chronic kidney disease, heart failure and type 2 diabetes

CI=Confidence interval; CKD=Chronic kidney disease; CKM=Cardiovascular-kidney-metabolic; CV=Cardiovascular; EF=Ejection fraction; ESKD=End-stage kidney disease; HbA1C=Glycated Hemoglobin; hHF=hospitalization for heart failure; HF=heart failure; HR=Hazard ratio; RRR=Relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitors; T2D=Type 2 diabetes.

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10 YEARS ANNIVERSARY forxiga

Clinical Trial Snapshot

by Migee Tang

Alcohol consumption is responsible for 2.6 million deaths per year, accounting for 4.7% of all global deaths[1]. It is also widely recognized that alcohol is a major risk factor for diseases such as cancers, cardiovascular diseases, and liver diseases, further contributing to alcohol-related morbidity[2-4]. Despite this significant burden, treatment rates for alcohol use disorder (AUD) remain below 10%, with only 2% of patients report receiving pharmacotherapy[5,6]. Semaglutide, a long-acting glucagon-like peptide 1 receptor agonist (GLP-1RA) known for its anti-diabetic and weight loss effects, has shown promise in reducing voluntary alcohol consumption preclinically, suggesting its potential as a pharmacotherapy for AUD[7,8].

The Trial[7]

Objective

A prospective, phase 2, randomized clinical trial to evaluate the effects of once-weekly subcutaneous semaglutide in non-treatment-seeking adults with AUD

Study Population

48 participants
(14 men, 34 women)

- Not seeking treatment for AUD
- 21 – 65 years
- Met AUD DSM-5 criteria in the past year
- No past use of GLP-1RA and other weight loss medications
- No past-year substance use disorder other than AUD

Females:

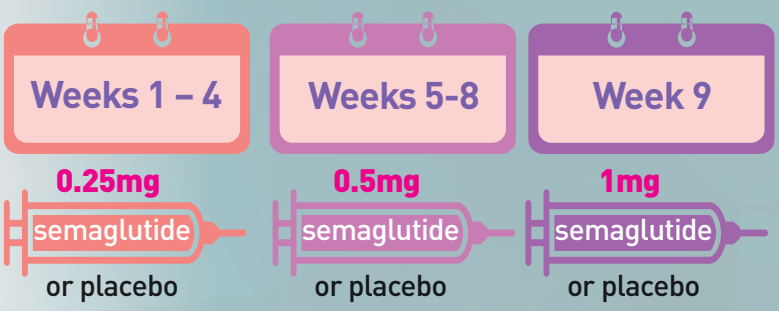
>7 standard drinks in a week with ≥2 heavy drinking episodes (≥4 drinks) in a week

Males:

>14 standard drinks in a week with ≥2 heavy drinking episodes (≥5 drinks) in a week

Trial Design

1:1 randomization to semaglutide or placebo arm



Slimming Down and Sobering Up – Fight Alcohol Cravings with Semaglutide

Primary Endpoint

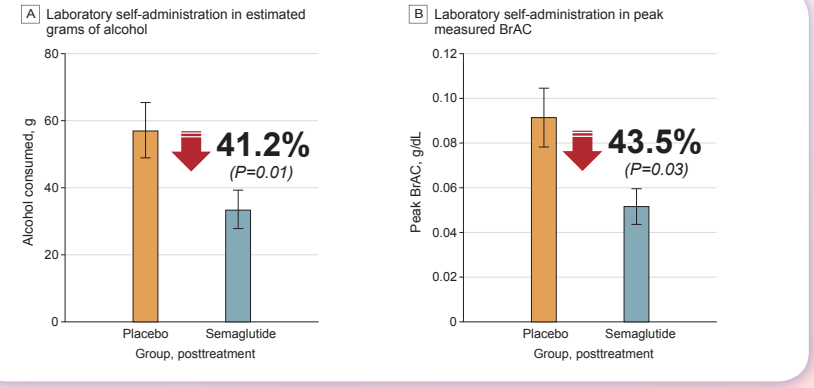
- Change in amount of alcohol consumed (grams & breath alcohol concentration (BrAC))
  - Measured by validated laboratory alcohol self-administration protocol

Participants provided option of drinks or monetary reward

Secondary Endpoints

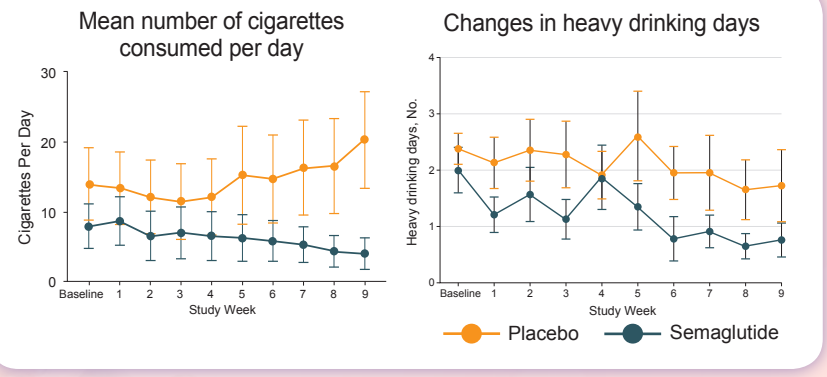
- Alcohol/cigarette demand
- Subjective responses to alcohol during alcohol administration
- Naturalistic drinking and smoking behaviours over treatment period

Significant reductions in post-treatment laboratory consumption in both grams of alcohol consumed and peak BrAC in the semaglutide group



Significantly greater reductions in cigarette demand (P=0.005) and number of heavy drinking days (P=0.04) in the semaglutide group

- No serious AEs, adverse interactions with alcohol, or treatment-related discontinuations recorded



Future Directions

- **Prospective studies with larger sample size and longer treatment durations**
- **Higher AUD severity in study population to reflect condition of most treatment-seeking samples**
- **FDA-accepted efficacy end points to support semaglutide as AUD therapy class**

AE, adverse events; **AUD,** alcohol use disorder; **BrAC,** breath alcohol concentration; **DSM-5,** Diagnostic and Statistical Manual of Mental Disorders; **GLP-1RA**, glucagon-like peptide 1 receptor agonist

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by Dr. Mohsin Roshan

Hidden Danger of Paediatric Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract (GIT) characterised by the repetitive inflammation of the GIT caused by an abnormal immune response[1]. Despite IBD is often described as a bimodal disease, it has recently gained attention since there has been an increase in the number of cases of paediatric IBD (pIBD) in children below the age of 15[2]. Due to the diagnostic delay and limited treatment options available for these patients, the risk of growth failure and long-term complications remain a serious parental concern[3]. This underscores the urgent and pressing need for improved treatment options to address the challenges of pIBD.

Gastroenterology

Navigating Through the Burden of Paediatric IBD

IBD is a chronic inflammatory disease of the GIT, divided into Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified[1]. The disease is characterised by the repetitive inflammation of the GIT caused by an abnormal immune response, and the disease distribution varies in each subtype. For instance, UC often affects the rectum (proctitis) but may extend into the sigmoid colon (proctosigmoiditis) or beyond (distal UC) or affect the entire colon up to the caecum (pancolitis). Contrarily, CD results in transmural ulceration, which means the inflammation extends through the entire thickness of the intestinal wall of any portion of the GIT, affecting the terminal ileum and the colon[4]. Despite IBD is often described as a bimodal disease with an incidence peak seen in those aged 15-25 and a second, smaller peak seen during the fifth to seventh decade in life[5], the disease has recently gained research interest since there has been an increase in the number of cases related to pIBD in children below the age of 15[2].

The factors driving this increase in pIBD cases remain uncertain. Some experts speculate that a combination of genetic predisposition, a diet that is typical of Westernised societies (referred to as 'Westernised diet'), poor generation of immune tolerance, and gut microbiota dysbiosis may possibly be the culprits[1]. The rising incidence of pIBD is likely to put more strain on the already burdened healthcare system, as these patients often present with a more severe phenotype, requiring more surgeries and escalated treatment regimens[1]. The diagnosis of IBD continues to be challenging, as it manifests with a variety of intestinal and extraintestinal symptoms that can present insidiously or in a fulminant manner. The diagnostic delay in pIBD is particularly concerning, as it can lead to an increased risk of complications, loss of opportunity to recover optimal growth, and a negative impact on overall psychosocial and physical development[6].

pIBD maybe driven by combination of genetic and environmental exposure

Unravelling the Diagnostic Challenges Related to Paediatric IBD

In up to 10% of paediatric cases, the distinction between CD and UC can be difficult. As the disease progresses, patients with IBD-unclassified may develop into either CD or UC. Furthermore, in a small proportion of children with IBD, UC may co-exist with primary sclerosing cholangitis (PSC-IBD) and these children may have a critical risk of developing colorectal cancer or cholangiocarcinoma[7]. Patients with IBD may present with non-classical signs of IBD, such as mild abdominal discomfort, lethargy, delayed puberty, and growth failure[3], which may delay the child's opportunity to recover optimal growth due to diagnostic delay[6]. The extent of the diagnostic delay for pIBD was evaluated in a systematic review by Ajbar *et al*. (2022) that included 24 paediatric studies that reported the overall median diagnostic delay ranged from 2.0-10.4 months for IBD, 2.0-18.0 months from UC and 4.0-24.0 months from CD. However, for approximately two-thirds of UC (68.8%) and CD (66.7%) studies, delay ranged from 2.0-

3.0 and 4.0-6.3 months, respectively. This highlights the crucial need for early diagnosis to prevent further complications.

The study found that children continued to wait for several months for a final diagnosis of IBD, and those with CD experienced longer delays than those with UC[3]. These findings demonstrate that diagnostic delays are the major contributing factor to the poor prognosis of the disease in children due to a lack of awareness among parents[8]. Apart from the diagnostic delay, patients who develop IBD during childhood are at higher risk for a more severe disease course and intestinal complications compared to adult-onset cases. As a result, this may be attributed to a longer lifetime risk, thus increasing the all-cause mortality risk secondary to GI cancers for children with IBD by up to threefold compared to children without IBD. Importantly, pIBD is also plagued by limitations in the therapeutic arsenal and psychosocial impact during the transition of children with IBD to adulthood[7]. Additionally, paediatric studies have suggested children exposed to antibiotics during their infancy may have a higher risk of developing IBD due to gut microbiome dysbiosis[9].

Diagnostic delay in pIBD is among the major contributing factor for a poor prognosis in children due to longer lifetime exposure

Antibiotics: A Double-Edged Sword in Paediatric IBD Incidence

Antibiotic treatment is sometimes required to treat infections, fistulas, abscesses in pIBD, and antibiotic therapy can influence the course of IBD by decreasing luminal bacteria concentrations and possibly altering the composition, favouring beneficial bacteria[10]. The effects of antibiotics use in the paediatric population, particularly during the first 5 years of life, and the risk of developing pIBD was evaluated in a nationwide cohort by Jawad *et al*. (2023). The study identified 1,927 paediatric IBD patients and 18,318 reference individuals from a National Patient Registry in Denmark between 1995 and 2018. Antibiotic exposure was defined as being prescribed antibiotics during the first 5 years of life[11]. Strikingly, the study found that oral antibiotic exposure during the first 5 years of life was associated with a higher risk of developing pIBD (hazard ratio [HR]= 1.33; 95% confidence interval [CI]: 1.2-1.5, p<0.0001). This finding underscores the need for caution use of antibiotic in this population. Interestingly, the risk escalated further in patients treated with ≥4 antibiotics prescriptions compared to those without antibiotic exposure (p<0.0001). Furthermore, broad-spectrum antibiotics increased the risk of pIBD more than narrow-spectrum antibiotics (p<0.0001), particularly in patients with CD (p=0.002), but not UC. These findings suggested that early antibiotic exposure was associated with an increased risk of pIBD, and repeated exposure increased the risk estimate further[11].

Not surprisingly, a pooled analysis by Mårild *et al*. (2024) evaluated childhood antibiotics use in early-life infection and the subsequent risk of developing IBD. The study included data from 103,046 patients (11,872 from Sweden, and 91,174 from Norway) with 395 patients diagnosed with IBD. Remarkably, the study revealed that the use of non-penicillin antibiotics at 1 to <3 years of age was associated with an increased risk of UC but not CD[12]. Similarly, Andersen *et al*. (2024) evaluated antibiotic exposure prenatally and the risk of developing pIBD before the age of 2 in 536,819 children with 797 identified cases of pBID in Norway from 2004-

2012 until the study's end on 31st December 2020. The study found that children exposed to antibiotics before the age of 2 were 1.3-fold more likely to develop pIBD than unexposed controls, and this association was only applicable to patients who developed CD but not UC[13]. Considering that all three Scandinavian studies have clearly highlighted the association between antibiotic exposure and subsequent development of pIBD, it is undeniable that broad-spectrum antibiotic use seems to be a common denominator and causative factor in pIBD development.

Children of the age 2 exposed to antibiotics were 1.3-fold more likely to develop pIBD than unexposed children

Treatment Transformation in Paediatric IBD

Despite recent treatment advances over the last few decades for adult IBD, the limited availability of new biologics remains in pIBD, necessitating the urgent need to optimise paediatric care in this area[14]. The unmet treatment need is confounded by a significant time lag of around 7 years seen between marketing authorisation being granted for IBD treatment. Furthermore, the time for the primary completion of pIBD clinical trials is often long due to the slow recruitment process, and this inadvertently leads to limitations on choices of treatment that can be used for pIBD in clinical settings[2]. Due to this inadequacy, it is estimated that the risk of needing surgery 10 years post-diagnosis among the pIBD population is approximately 1 in 3 for CD and 1 in 5 for UC[15]. The current guidelines from both the European Crohn's and Colitis Organisation (ECCO) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) emphasise early intervention with biologics for children at risk of severe disease or those who are unable to achieve remission with exclusive enteral nutrition or corticosteroids[8]. ECCO-ESPGHAN guidelines also recommend considering anti-TNF therapy for maintenance and induction of remission in patients with delayed growth or severe disease presentations. Similar recommendations are echoed by the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), in addition to the use of combination therapy to enhance treatment durability and reduce the risk of antibody formation against biologics[8].

Not surprisingly, only infliximab and adalimumab are approved by the Food and Drug Administration (FDA) as treatment options for pIBD. Despite this, other agents such as vedolizumab (VDZ), a humanised monoclonal antibody that selectively binds to the alpha-4-beta-7 integrin, is currently being trialled. However, the long-term efficacy and safety of VDZ as maintenance therapy in the paediatric population have not been evaluated. Thus, VEDOKIDS, which was a multicentre, prospective cohort study in children <18 years with CD, UC or IBD unclassified with cohorts from 17 centres in 6 countries (Israel, the United States of America [USA], Italy, Ireland, Denmark, and Slovenia). A total of 137 patients (47% with UC, 47% with CD and 7% with IBD-unclassified) were prospectively followed up to 54 weeks and the primary outcome was complete remission (CR) at week 54, defined as CR (weighted Paediatric Crohn's Disease Activity Index [wPCDAI] of <12.5 points in CD and Paediatric Ulcerative Colitis Activity Index [PUCAI] of <10 in UC) without the need for surgery, exclusive enteral nutrition for children with CD, or steroid (steroid-free and exclusive enteral nutrition-free clinical remission) plus C-reactive protein (CRP) concentration lower than 1.5 times the upper limit of normal (ULN) of 0.5 mg/dL. Conspicuously, the PUCAI score in children with UC decreased from 25 at baseline to 5 after week 54, and the median wPCDAI score also decreased from a baseline of 35 to 13 at week 54. Improvements in the disease activity were significant by week 6, and 25% of children with CD and 47% with UC or IBD unclassified remained in CR. The study supported the use of VDZ in pIBD for maintaining remission, more so in UC than in CD[16].

Take Home Message

The availability of new biologics holds promise, but further paediatric-focused research and updated clinical guidelines are required to reduce the disease burden of pIBD in the paediatric population.

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HK-EQ-VB-23J-01

by Dr. Roy Lau

The Establishment of Consensus on the Management of Lupus Nephritis for the Asia-Pacific Region

Lupus nephritis (LN) is one of the most common organ manifestations of systemic lupus erythematosus (SLE), affecting more than 50% of patients[1], whereas up to 20% of patients with LN eventually progress to end-stage renal disease (ESRD)[2]. Of note, a majority of patients with LN are younger than 50 years[3]. This highlights the substantial disease burden and socioeconomic impact of the disease. Although several clinical guidelines for managing LN have been developed in European countries[4] and the United States (U.S.)[5], the differences in clinical and socioeconomic factors between Asian and non-Asian patients may influence therapeutic decisions in managing LN. To cater the specific requirements in the Asia-Pacific region, the SLE special interest group (SIG) of the Asia-Pacific League of Associations for Rheumatology (APLAR) has recently published the consensus statements for managing LN specialised for the region[6].

A Glance at the Clinical Features of LN

SLE is a multisystem autoimmune disease with a relapsing and remitting course, whereas kidney involvement is common and remains a major cause of mortality and morbidity. LN can be asymptomatic with urinalysis, renal function and 24 h-proteinuria within the normal range. However, the disease may also be highly symptomatic and characterised by urinary abnormalities, such as haematuria, and more overt presentations, including acute nephritic syndrome and rapidly progressive renal failure[7]. Moreover, other clinical features, such as elevated serum creatinine and hypertension, can be developed in some cases of LN[8]. The symptoms of LN often occur at the same time or shortly after lupus symptoms[9].

Given the variability of clinical manifestations of LN, determination of serum creatinine, estimated glomerular filtration rate (eGFR) and urinalysis for urinary albumin/creatinine ratio (uACR), urinary protein/creatinine ratio (uPCR), and/or urinary sediment, can be performed to indicate LN-related abnormalities[10]. Remarkably, renal biopsy remains the gold standard for diagnosing LN when proteinuria is identified. Renal biopsy provides information on the degree of inflammation and the extent of damage and helps rule out other causes of proteinuria or renal dysfunction in SLE patients[1].

The Impacts of Racial and Ethnic Differences on LN Outcomes

The burden of LN shows race and ethnicity-related disparities. According to a retrospective analysis of the California Lupus Surveillance Project (CLSP) by Maningding *et al*. (2020), Black (prevalence ratios [PR]: 1.74), Asians/Pacific Islanders (API, PR: 1.68), and Hispanic (PR: 1.35) SLE patients demonstrated significantly increased prevalence of renal manifestations versus Whites ($p<0.001$ for all). Furthermore, both Blacks (PR: 1.09, $p<0.001$) and APIs (PR: 1.07, $p<0.05$) had increased prevalence of hematologic manifestations. The results also indicated higher risks of developing antiphospholipid syndrome

among APIs (hazard ratio [HR]: 2.5) and Hispanics (HR: 2.6) than Whites. Essentially, APIs were reported to have the highest risk of developing LN (HR: 4.3), followed by Blacks (HR: 2.4) and Hispanics (HR: 2.3), as compared to Whites[11].

Apart from disease burden, the randomised controlled trial (RCT) by Appel *et al*. (2009) reported that serious infections and deaths developed in a substantial proportion of Asian patients with LN treated with higher doses of mycophenolate mofetil (MMF)[12]. This highlights the potential risk of adverse responses to immunosuppressive therapies among Asian patients.

On the other hand, it is crucial to realise the impact of socioeconomic factors on the management of LN in the Asia-Pacific region. Accordingly, the organisation of healthcare structure and delivery, financial limitations, education level and compliance of patients, as well as environmental and climate factors differ significantly among Asian regions. These factors would alter patients' access to standard-of-care and clinicians' treatment decisions[13].

Interestingly, the belief about medicines among Asian SLE patients has been reported to be different from the British/Irish Whites in that the former were more concerned about the toxicities of drug therapies, particularly immunosuppressive medications[14]. Hence, patients of South Asian origin tend to terminate immunosuppressive therapy sooner than those in Northern Europe[15].

By virtue of the specific epidemiology, socioeconomic and cultural background, patient adherence, and the pattern of treatment response regarding LN in Asia-Pacific region, a set of consensus statements specialised for managing LN in this region is highly desirable.

Formulating the Consensus for Managing LN in the Asia-Pacific Region

The consensus statements on the management of LN for the Asia-Pacific region were formulated by the SLE SIG established under the Scientific Committee of the APLAR. The core group reviewed the literature by means of a PubMed search using keywords derived from a set of Population Intervention Comparison Outcome (PICO) questions. An initial list of 56 statements was drafted and selected by the core group members based on the search results and clinical practice[6].

The level of evidence and strength of recommendation of the proposed statements were evaluated in 3 rounds of Delphi exercise, which involved anonymous voting and feedback done via an online platform by 46 medical practitioners, including 31 rheumatologists, 13 nephrologists, 2 renal histopathologists, from 21 Asia-Pacific regions, and 2 LN patients. The agreement score was derived from a Likert scale in which participants were required to vote for the level of agreement with the statements. Statements with agreement by at least 80% of the voting members reached consensus[6].

After the Delphi exercise, 48 consensus recommendations were finalised, which were categorised into overarching principles, diagnosis and monitoring, initial and subsequent therapies, pure membranous LN, patients at risk of renal progression, adjunctive therapies and management of comorbidities, and renal replacement therapy[6].

Highlights of the APLAR Consensus on the Management of LN

Regarding the overarching principles in LN management, the consensus advocated that a shared decision between patients and physicians is required,

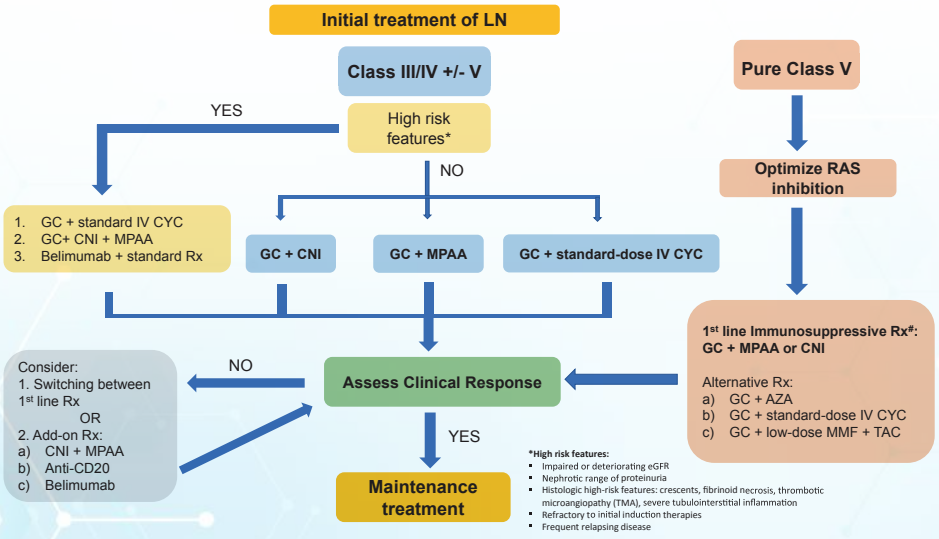

Figure 1: *Initial treatment of LN recommended in APLAR Consensus[6], IV: intravenous; MPAA: mycophenolic acid analogue; Rx: treatment; TAC: tacrolimus*

whereas the goals of treatment and patient adherence are underscored. Besides, the consensus recommended monitoring LN using clinical and laboratory parameters. Additional tests are recommended if a flare-up is suspected. In particularly, kidney biopsy is suggested to characterise the disease's conditions[16].

A major focus of the consensus is on the initial and subsequent therapies of LN. For initial treatment of LN, a combination of glucocorticoids (GCs) with cyclophosphamide (CYC), mycophenolate mofetil (MMF), or calcineurin inhibitors (CNIs) is recommended as the first-line options. Additionally, an upfront combination of immunosuppressive drugs and biological agents may be considered in patients at significant risk of disease progression and renal function deterioration. For refractory diseases, switching or add-on among different immunosuppressive agents, including biological agents, may be considered (**Figure 1**)[6].

The consensus recommended that maintenance therapy of LN should follow induction regimens when the target response is achieved and continue for at least 3 years to reduce the risk of renal flares. Remarkably, lower-dose MMF and azathioprine (AZA) can be considered, whereas MMF maintenance should follow induction by the same drug. On the other hand, low-dose prednisolone may be continued at a dose of 5 mg/day or less, and the decision to discontinue GCs and the tempo for tapering should be individualised (**Figure 2**)[6].

The use of adjunctive therapies and the management of LN-related comorbidities are also covered in the consensus. For instance, the universal use of hydroxychloroquine in all SLE patients is recommended. Moreover, regardless of hypertension status, the renin-angiotensin system (RAS) blockade is recommended for all LN patients. Essentially, lifestyle modification, anticoagulation, control of cardiovascular risk factors, prevention of osteoporosis, drug-related toxicities, as well as infective complications are advocated in the consensus statements. Last but not least, the consensus addresses recommendations on renal replacement therapies, the use of immunosuppressive agents during dialysis, and the optimal timing for kidney transplantation[6].

Given the comprehensive coverage of opinions on managing LN by clinical experts and patients from various Asia-Pacific regions, the 2024 APLAR consensus on the management of LN is expected to provide holistic guidance tailored for physicians managing LN patients in the region.

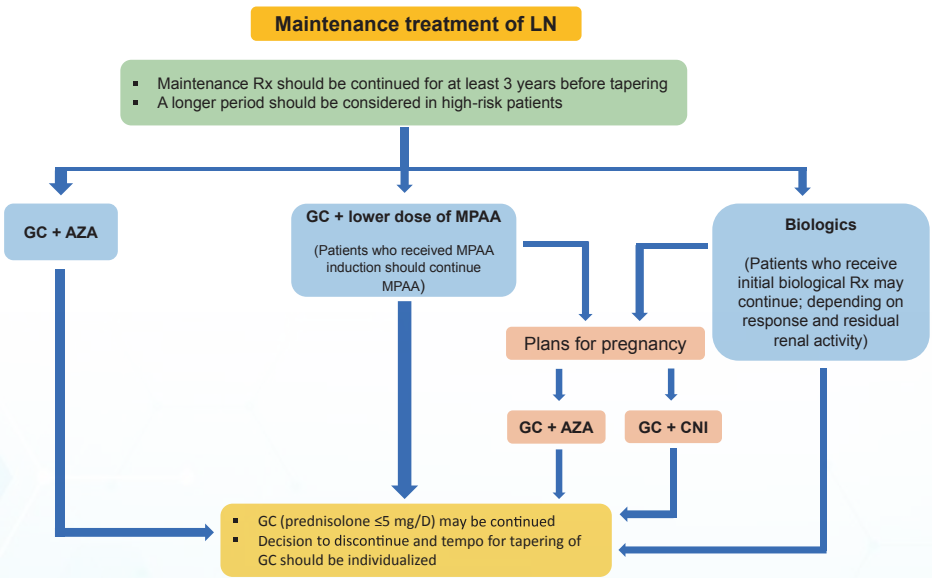

Figure 2: Algorithm for maintenance treatment of LN[6]

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by Dr. Feng Xue

Hand, Foot and Mouth Disease and Enterovirus 71 Vaccination in Children – Experience from Mainland China

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- *Chairman, Children's Health Care Committee, Guangdong Preventive Medicine Association, China*
- *Vice-Chairman, Precision Vaccine Immunization Branch, Guangdong Precision Medicine Application Society, China*
- *Vice-Chairman, Precision Diagnosis & Treatment for Vaccine Adverse Reactions Branch, Guangzhou Medical Association, China*
- *Vice-President, Guangzhou Preventive Medicine Association, China*

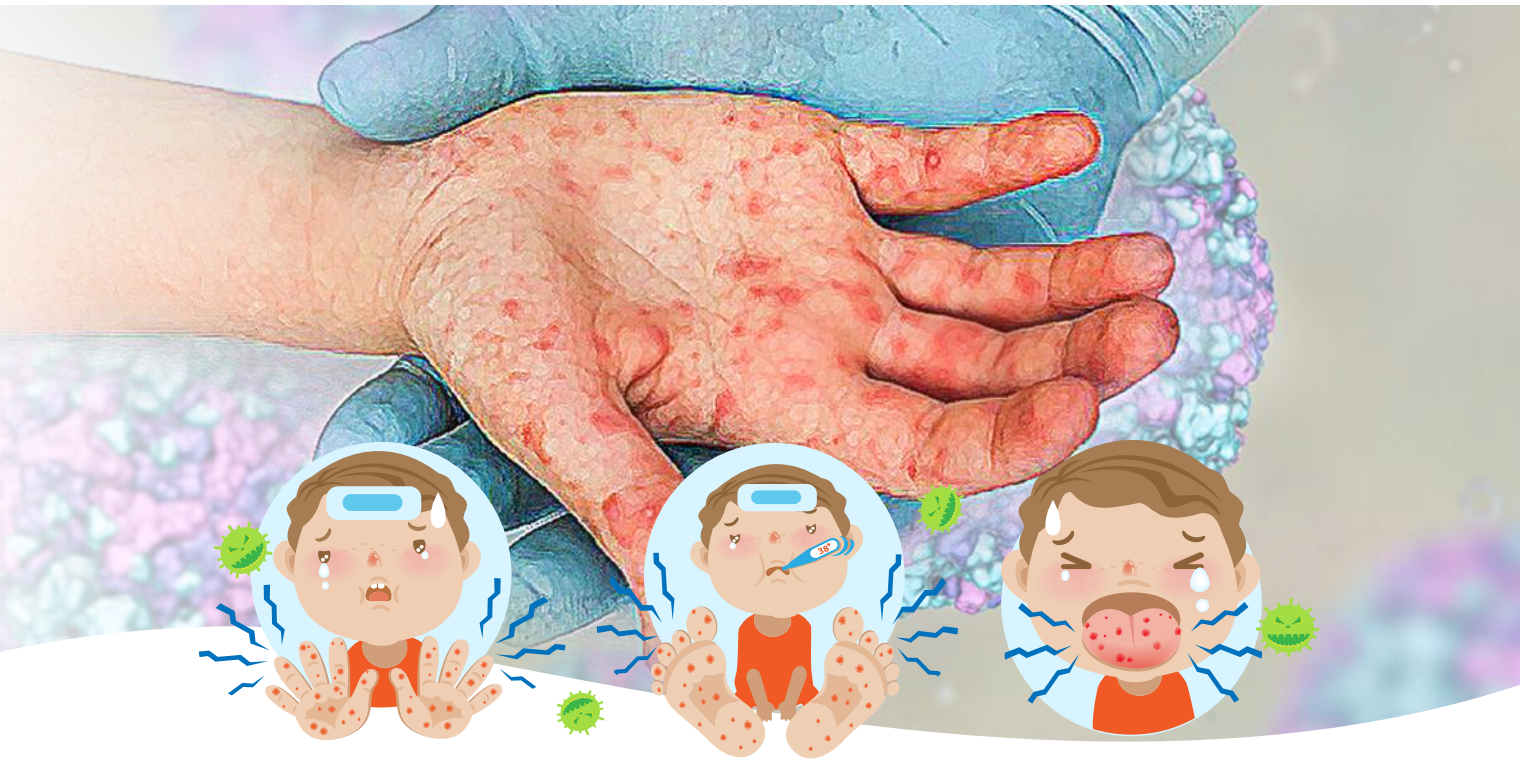
The hand, foot, and mouth disease (HFMD) is a common infectious disease in children under 5 years of age characterized by an oral enanthem and a macular, maculopapular, or vesicular rash of the hands and feet (and possibly other locations such as buttocks).[1,2] It is caused by a group of enteroviruses (EV),[1-3] and enterovirus 71 or enterovirus A71 (EV71) is among the most common causative agents associated with severe manifestation of the disease.[3,4] Although there is no specific treatment for the HFMD, preventive efforts are being made through vaccination.[5] An inactivated EV71 vaccine, which obtained Marketing Authorization in China in December 2015, has been shown to provide a high level of protection against EV71-related HFMD.[6,7*] To understand the recent development in EV71 prevention, the 11th Asian Congress of Pediatric Infectious Disease in Hong Kong invited Professor Dandan Hu, a renowned pediatric specialist in China, to discuss issues related to HFMD caused by EV71, as well as sharing certain clinical findings, particularly on the efficacy and safety of EV71 vaccination in mainland China.

Introduction

In recent years, HFMD has been widely recognized as a highly infectious disease in children globally, especially in the Asia-Pacific area.[8] Furthermore, HFMD is caused by a wide variety of enteroviruses, among which EV71 is the major pathogen that leads to severe HFMD, central nervous system (CNS) injury and even death.[8] Here, Prof. Hu highlighted that the EVs are members of the *Enterovirus* genus in the family *Picornaviridae*, consisting of 13 species: EV A–J and rhinovirus A–C.

The EV-A species plays a major role in causing the HFMD, followed by EV-B. EV-A consists of 25 serotypes including the EV71, [9] and the C4 sub-genotype of EV71 has been the most dominant sub-genotype circulating in mainland China since 1998.[10]

It is usually a self-limiting infection, but is highly contagious and efficiently propagated to household contacts by oropharyngeal secretions or fecal- oral transmission.[11] The incubation period ranges from 3-5 days,[12] and the disease typically affects young



children under the age of five years, characterized by maculopapular rash or blisters on the hands, soles and buttocks, in addition to painful ulcerative lesions in the mouth.[11] These symptoms typically resolve spontaneously within a few days without complications. Nevertheless, infection with EV71 can be catastrophic since EV71 is a neurotrophic virus that can cause CNS complications including aseptic meningitis, cerebella ataxia, poliomyelitis-like paralysis, acute brain encephalitis, and fulminant neurogenic pulmonary edema associated with high mortality.[11] Here, Prof. Hu commented that a higher incidence of severe complications, including brainstem encephalitis, acute flaccid paralysis, neurogenic pulmonary edema, pulmonary hemorrhage, shock, and rapid death has been reported during the EV71 outbreaks.[13] She added that EV71 was responsible for a series of outbreaks across the Asia-Pacific region since the 1990s.[14,15] The largest Asia-Pacific epidemic occurred in China in 2008, when approximately 490,000 infections and 126 deaths in infants and young children were reported.[16] A national HFMD surveillance system was eventually set up following the epidemic, and the surveillance data revealed that the EV71 related infections accounted for up to 44% of all laboratory- diagnosed cases, 40% of mild cases, 74% of severe cases, and 93% of deaths.[17]

Unfortunately, there are no guideline directed or established antiviral treatments for HFMD. Vaccination may offer the best option for the disease control,[6,7] and Prof. Hu then introduced the vero cell-based E71 inactivated vaccine for children aged 6-71 months.[7]

Cross-Neutralization and Robust Protection Against EV71 Sub-Genotypes

The inactivated EV71 vaccine is based on the C4 sub-genotype of EV71, and received approval in December 2015 for use in China,[7*] according to Prof. Hu. Studies on EV71 vaccines showed that, the C4-based vaccine, in particular, exhibited a high cross-neutralizing antibody titer against prominent global EV71 sub-genotypes (A, B0-B5, C1, C2, and C5), compared to the B4-based vaccine (C4 and B5) in children, indicative of a robust protection against HFMD caused by different strains.[18,19]

Prof. Hu then shared the data of a randomized, double-blind, placebo- controlled, multicenter trial which included 10,007 healthy infants and young children (6–35 months of age), who were randomized in a 1:1 ratio to receive two intramuscular doses of either the inactivated EV71 vaccine or placebo, 28 days apart. Patients were followed up for 12 months and the primary endpoint was the occurrence of EV71-associated HFMD or herpangina. The inactivated EV-71 vaccine efficacy against EV71-associated HFMD or herpangina was 94.8% (95% confidence interval [CI], 87.2 to 97.9; $P < 0.001$) compared to the placebo. Moreover, vaccine efficacy against EV71- associated hospitalization (0 cases in inactivated EV71 vaccine group vs 24 cases in placebo group) and HFMD with neurologic complications (0 cases in EV71 vaccine group vs 8 cases in placebo group) were both 100% (95% CI, 83.7 to 100 and 42.6 to 100, respectively). Serious adverse events were comparable between the inactivated EV71 vaccine group and the placebo group (2.2% vs 2.6%).[6]

In relation to the safety of the inactivated EV71 vaccine, Prof. Hu shared the data from a multicenter observational study that included 40,000 children, which reported an overall adverse reaction incidence of 1.08%, with most reactions being mild or moderate, such as redness at the injection site and fever. Remarkably, there was no serious adverse events reported, substantiating the vaccine's robust safety even in large-scale use.[20]

Rapid and Persistent Immunity

The longevity of antibodies induced by the inactivated EV71 vaccine has not previously been well reported. Therefore, Pro. Hu shared the short- and long-term effects of the inactivated EV71 vaccination from two studies. The first study was by Wang et al. (2020) that evaluated the short-term neutralizing antibodies against EV71 and EV71-immunoglobulin M (IgM) after inactivated EV71 vaccine injection. The study included 120 healthy infants aged 6–35 months who were randomized 1:1:1 to provide a second blood sample at day 10, day 20 or day 30 after the first vaccine dose, respectively. The study demonstrated a rapid immune response against EV71 after first inactivated EV71 vaccine dose, with antibody titers ≥1:8 observed in 89.19% of participants (95% CI: 74.58–96.97%) at day 10 and as high as 100% at day 60 (**Figure 1**).[21]

Similarly, the 5-year immunity data conducted by Hu et al. (2018) on inactivated EV71 vaccine in 211 participants (106 vaccine subjects and 105 placebo subjects) showed the seropositive rate (SR) of the neutralizing antibodies at 5 years remained at 94.34% in the vaccinated subjects with the geometric mean titer (GMT) of 141.42 compared to only 71.43% SR and a GMT of 71.83 among the

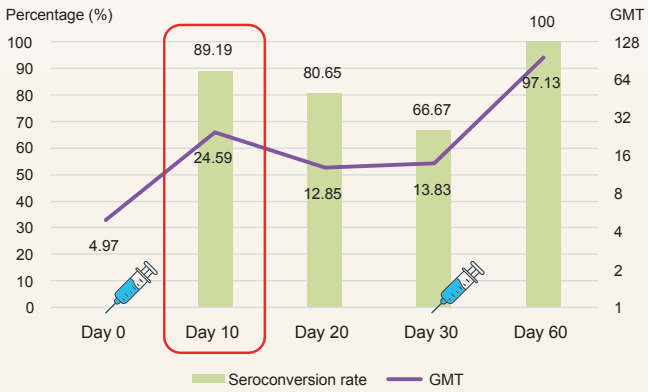


Figure 1: Seroconversion rate and GMT between Day 0 and Day 60.[21] GMT, geometric mean titer.

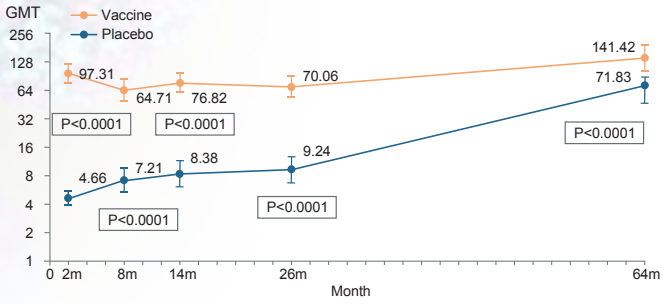


Figure 2: GMT between Day 0 and Month 64.[22] GMT, geometric mean titer.

placebo group (**Figure 2**).[22] The findings suggest that inactivated EV71 vaccine induces persistent immunity within 5 years following the primary vaccination.[22]

Prof. Hu added that the EV71 vaccine can be co-administered with other routine immunizations, such as hepatitis B, Group A meningococcal polysaccharide vaccine, measles-mumps-rubella (MMR) vaccines, and epidemic encephalitis B vaccine, without increasing the risk of adverse reaction incidence or compromising immunogenicity.[23,24]

Health Benefits of EV71 Vaccination

The 2021 statistical data showed that the cumulative EV71 vaccination coverage was estimated to be 25% in birth cohorts in China, and the coverage rates varied by region in relation to the HFMD prevalence and disposable income per capita. Interestingly, the national EV71 vaccination coverage rates ranged from about only 3% in Xinjiang to 56% in Shanghai, China.[25]

Since the introduction of the EV71 vaccine, HFMD cases and deaths have drastically declined in China. There was an 85% reduction in deaths related to HFMD caused by EV71 between 2016 and 2020.[26] Studies also showed a shift in the age distribution of HFMD cases after the vaccination, with the median age increasing from 2.24 to 2.81 years, suggesting that vaccination is altering the susceptible population. Additionally, recent epidemiologic studies revealed a 28.3% decrease in the proportion of HFMD patients infected with EV71 and a staggering 60.7% reduction in severe cases. Similarly, severe illnesses and mortality rates have dropped by 62.2% and 83.8%, respectively. In terms of geographical distribution, the HFMD cases were previously concentrated in central, southern and eastern parts of China and the cumulative incidence of HFMD has declined dramatically after the introduction of EV71 vaccines in these areas,[27] Prof. Hu added.

A study conducted in Guangdong aimed to evaluate the difference of EV71 infections with and without

vaccination. The study used a model to predict a monthly counterfactual incidence of EV71-associated HFMD cases from 2017 to 2019, then compared the counterfactual incidence with observed incidence to estimate the impact of the EV71 vaccination program. This study showed that cities with higher vaccination coverage saw a 41.4% reduction in HFMD cases caused by EV71, with an estimated 26,226 cases averted. Moreover, the study also observed an indirect protection (herd immunity) as the number of HFMD patients aged 6–14 years, who were not vaccinated, was reduced.[28] Prof. Hu added that the proportion of HFMD cases caused by EV71 has steadily declined in Hefei, the capital of Anhui, China since 2017, and the incidence of EV71 remained at a very low level, as shown in another study. Interestingly, in this study there was an observed inverse correlation between EV71 vaccination coverage and the decline in EV71 positivity (**Figure 3**).[29]

Prof. Hu briefly highlighted that the HFMD costs range from $366.50 United States dollars (USD) per patient with mild cases to $2,355.89 USD per patient with severe cases. More worryingly, the annual economic losses attributed to HFMD ranged from 7.03 million USD to 13.31 million USD.[30] Between 2016 and 2018, the introduction of EV71 vaccines averted an estimated economic burden of 30.11 million Chinese yuan in Beijing, China.[31]

In summary, HFMD, especially that caused by EV71 can pose a severe health risk to children with substantial economic burden. Vaccination may offer protection against the disease. Currently the inactivated EV71 vaccine is approved in China for pediatric population[7*] and has demonstrated promising efficacy, as well as safety against EV71-associated HFMD with immunity lasting over 5 years. In light of these findings, expansion of EV71 vaccination coverage is urgently needed to reduce incidence of EV71- associated HFMD.

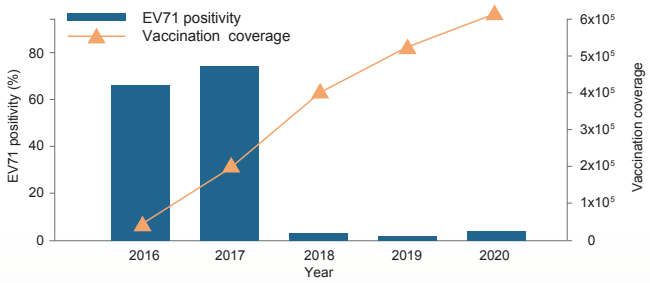


Figure 3: *EV71 vaccination coverage and EV71 positivity.[29] EV71, enterovirus 71.*

*The inactivated EV71 vaccine obtained Marketing Authorization in mainland China in December 2015; but has not been registered in Hong Kong.[7]

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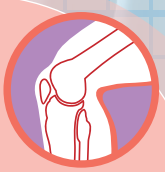
by Dr. Mohsin Roshan

Geniculate Artery Embolisation for Knee Osteoarthritis

Background on Knee Osteoarthritis

Osteoarthritis (OA) is a common degenerative joint disease that causes progressive deterioration of joint cartilage and the underlying bone. Knee OA (KOA) is a common debilitating disease among older adults, affecting nearly 1.27 million individuals aged ≥65 years in Hong Kong since 2018 and expected to double by 2038[1]. KOA pain is often be debilitating and recent use of genicular artery embolisation (GAE) hope to change the treatment paradigm in KOA patients[2]

LipioJoint-1, a Prospective, Single-arm, Open-label Trial



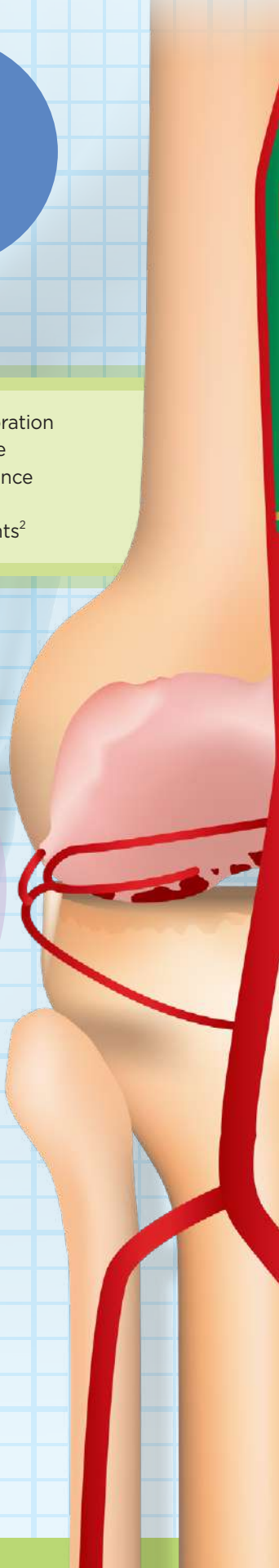
Objective

To evaluate the safety and efficacy of transient GAE using an ethiodised oil-based emulsion for the treatment of KOA

Study Design

LipioJoint-1, a prospective, single-arm, open-label trial

22 participants* from 2 academic hospitals between March 2021 and June 2022



Inclusion criteria

- ✔ Primary KOA according to the American College of Rheumatology classification and of Kellgren-Lawrence (KL) grade ≥2
- ✔ Visual analogue scale (VAS) pain score ≥ 40 mm despite analgesic medication for at least 3 months
- ✔ Failure of intolerance of or patients unwilling to take opioid treatment
- ✔ Failure or refusal of intra-articular corticosteroid injection
- ✔ Patient not eligible for surgery (or refusing surgery)

Outcomes

- The primary outcome was the rate of serious adverse events attributed to GAE within one month.
- Secondary outcomes included immediate technical success rate (success of catheterisation and embolisation of at least one target artery), number of adverse events, rate of responders, rate of participants reaching the patient acceptable symptom state defined as a VAS score of < 32.3 mm, and questionnaire scores at follow-up

Results

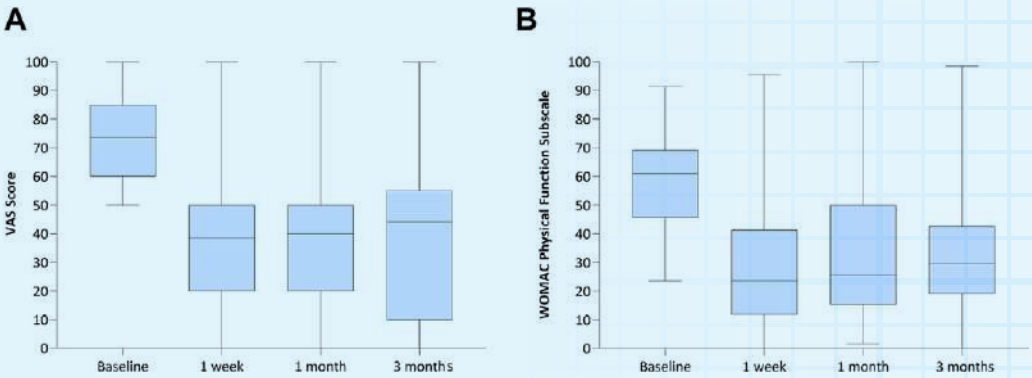
100% immediate technical success rate

Mean VAS pain score change

74.4 ± 16.5 (SD) mm

to **37.2 ± 26.7** (SD) mm at 3 months (p<0.001)

At 3 months, 16 out of 22 participants (73%) were responders



*Change in visual analog scale (VAS) pain score **(A)** and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) function score **(B)** over the three-month follow-up period. Symptoms are improved when scores decrease. WOMAC function score is normalized to 100 (score ranging from 0 to 100 mm).*

Conclusion

GAE using an ethiodised oil-based emulsion is safe and improves pain and function in participants with KOA for at least 3 months.

* 13 females, mean age, 66 ± 9 (standard deviation [SD]) were included and underwent GAE. Emulsion consisted in a mixture of ioversol and ethiodised oil (ratio 1:3, respectively) prepared extemporaneously.

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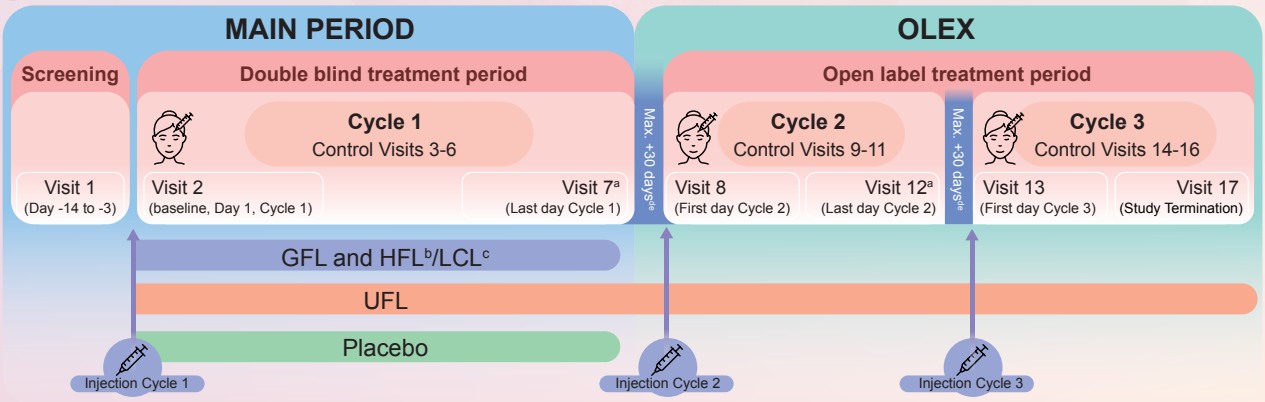
by Dr. Mohsin Roshan

Rediscover Youthful Radiance with Incobotuliniumtoxin A

Treatment with botulinum neurotoxin Type A (BoNT-A) is effective and predictable aesthetic procedure, particularly for the facial wrinkles. It accounts for 39% of the total top nonsurgical procedure with 3.9 million administrations in United States (U.S.) since 2022. Incobotulinumtoxin A (INCO), a formulation of BoNT-A that is highly purified without complex proteins; therefore, a lower risk of treatment failure and lower foreign protein load delivery. The safety and efficacy of INCO was evaluated in a 2 phase III studies for treating UFLs[1].

Objective: Aim of the study was to evaluate the safety and efficacy of simultaneous IM injections for UFLs. Longer-term safety and efficacy were assessed in OLEX

Study Design for ULTRA I and ULTRA II[1]:



[a] *Visit 7 (end-of-Cycle 1 visit) and Visit 8 (Cycle 2 baseline visit), as well as Visit 12 (end-of-Cycle 2 visit) and Visit 13 (Cycle 3 baseline visit) were performed on the same day if all eligibility criteria were met.*

[b] *In ULTRA I, GFLs and HFLs were treated with INCO.*

[c] *In ULTRA II, LCLs were treated with INCO.*

[d] *If the eligibility criteria were not fulfilled, an eligibility reassessment for entry into the next cycle at an optional visit within 30 days if possible was required.*

[e] *If a participant fulfilled the eligibility criteria at an additional eligibility visit, this visit was combined with the next injection visit.*

GFLs, glabellar frown lines; HFLs, horizontal forehead lines; LCLs, lateral canthal lines; OLEX, open-label extension; UFLs, upper facial lines.

Study Participants and Treatment[1]:

Participants:

Participants: Healthy participants (≥18 years) with moderate-to-severe GFLs, HFLs, and symmetrical LCLs at maximum contraction on the 5-point Merz Aesthetic Scales (MAS) were randomised 2:1:1 to receive up to 64 units of INCO in the main period of each trial.

Treatment groups:

UFL treatment group (Group U):
-20U INCO in GFLs
-20U INCO in HFLs
-24U INCO in LCLs

Placebo treatment group (Group P):
-Placebo in all 3 facial areas

GFL and HFL treatment group (ULTRA I, Group G&H):
-20U INCO in GFL
-20U INCO in HFL
-Placebo in LCL

LCL treatment group (ULTRA II, Group L):
-12U INCO in right LCL
-12U INCO in left LCL
-Placebo in GFL and HFL

Primary efficacy endpoints:

Proportions of GFL, HFL, and LCL responders, defined as a MAS score for the respective area of 0 (no), or 1 (mild) and a ≥2-grade improvement from baseline to Day 30, as assessed by both investigator and participant

Results[1]:

INCO treatment was significantly more effective than placebo (p<0.0001) for both primary and secondary* endpoints. No new safety concerns identified

(A) *Baseline GFLs.* ***(B)*** *Day 30 GFLs.* ***(C)*** *Baseline LCLs.* ***(D)*** *Day 30 LCLs[1]. GFLs, glabellar frown lines; LCLs, lateral canthal lines. Red arrows showing pre- and post-effects of the injection.*

Conclusion[1]:

In **ULTRA I** and **ULTRA II**, the safety and efficacy of INCO for simultaneous treatment of moderate-to-severe UFLs, were demonstrated, with significant improvements across all primary and secondary endpoints vs placebo

*Secondary endpoints: There were 7 key secondary efficacy endpoints: endpoints 1-3 were the proportion of participants with a score of 0 (no) or 1 (mild) on the MAS (as rated by the investigator) for GFLs, HFLs, and both the left and right LCLs at maximum contraction, respectively, at Day 30 of the MP; endpoints 4-6 were the proportion of participants with a score of 0 (no) or 1 (mild) on the MAS (as rated by the participant) for GFLs, HFLs, and both the left and right LCLs at maximum contraction, respectively, at Day 30 of the MP; endpoint 7 was the GAIS score as assessed by the participant at Day 30 of the MP[1].

Scan For PDF

Abbreviations

G1, group 1; G2, group 2; G3, group 3; GFLs, glabellar frown lines; HFLs, horizontal forehead lines; MP, main period;LCLs, lateral canthal lines; OLEX, open-label extension; UFLs, upper facial lines.

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by Dr. Mohsin Roshan

Usher a New Era for the Management of Acute Myocardial Infarction with SGLT2 Inhibitors

Heart diseases such as acute myocardial infarction (AMI) is among the leading cause of death and affects around 3 million individuals globally[1]. AMI is driven by atherosclerotic plaque, and post-myocardial infarction (pMI), the risk of developing heart failure (HF) increases by 50-60%[2]. Notably, the sodium-glucose cotransporter 2 inhibitor (SGLT2i), an antidiabetic treatment that has revolutionised the treatment for HF and chronic kidney disease (CKD), has shown a potential role in reducing the risk of hospitalisation for heart failure (HHF) in AMI patients and patients with other cardiac conditions.

Understanding the Burden of Heart Disease

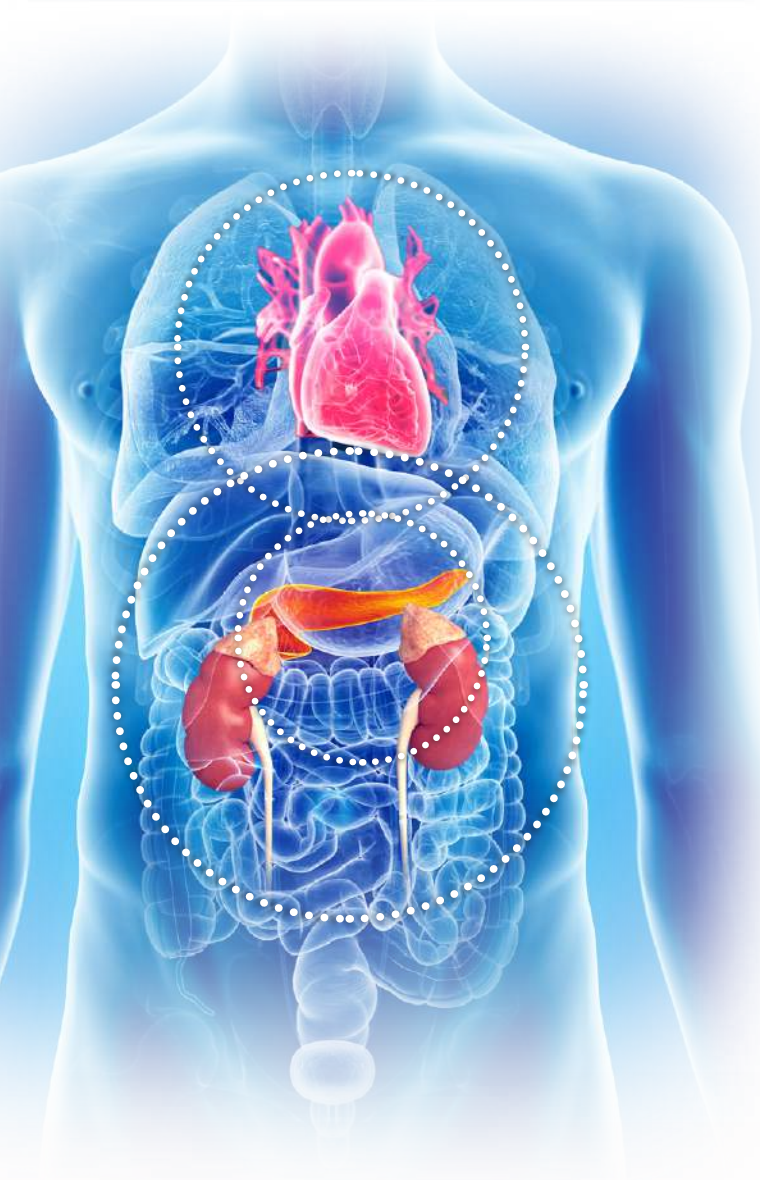
Heart diseases such as AMI is among the leading cause of death in the developed world. The disease affects around 3 million individuals globally, with more than 1 million deaths recorded in the United States (US) annually[1]. Locally, heart disease is the third leading cause of death in Hong Kong, and according to the World Health Organisation (WHO), 80% of premature heart attacks and strokes are preventable[3]. Heart diseases such as AMI can be divided into non-ST elevation myocardial infarction (NSTEMI) or, ST-segment elevation myocardial infarction (STEMI) or unstable angina, which may resemble that of an NSTEMI but with normal cardiac markers[1]. AMI typically occurs due to a decrease in the coronary blood flow secondary to atherosclerotic plaque rupture, leading to insufficient oxygen supply to the heart muscles. Not surprisingly, 70% of all fatal AMI cases are attributed to the occlusion caused by the atherosclerotic plaques[1] and post-MI; the risk of developing HF increases by 50-60% in these patients[2].

HF is a global public health concern and a significant economic burden. Despite recent treatment advances, the use and dosing of guideline-directed medical therapy (GDMT) in patients with HF remains suboptimal[4]. This was highlighted in the RED-HEART study, a multicentre, cross-sectional and observational study that included HF patients in the outpatient setting from 19 cardiology centres between August 2023 and December 2023. The study demonstrated that only 48.1% of patients among the 1,923 patients with HF received the SGLT2i, a drug shown to be beneficial in patients with different spectrum of HF ejection fractions[5]. Considering AMI still represents the primary cause of de novo HF as it is associated with significant mortality and morbidity[6], treatment and prevention remain the crucial in reducing the prevalence of HF.

AMI is the leading cause of death, affecting around 3 million individuals globally

SGLT2-Inhibitors: One Pill, Countless Cardiorenal Benefits

Despite SGLT2i being an antidiabetic treatment, it has been shown to improve cardiovascular and renal outcomes, regardless of the diabetic status among patients[7]. Considering renal disease such as chronic kidney disease (CKD) is present in > 30% of patients with AMI and together, these conditions has been associated with a worse prognosis[8], the use of SGLT2i may offer therapeutic benefits in patients with AMI and other cardiac pathologies. For instance, SGLT2i has also been shown to reduce the risk of atrial fibrillation (AF),



according to a systematic review and meta-analysis by Zheng *et al*. (2022) based on 20 randomised trials involving 63,604 patients. The study reported that patients treated with was associated with a lower risk of AF, but not stroke, regardless of their diabetic status[9]. Nonetheless, these findings were not substantiated in other studies that showed SGLT2is exerting no beneficial effect in preventing AF, regardless of the follow-up duration, type or dose of the drug or the patient population[10].

Interestingly, AF often coexists in patients with AMI and incidence of AMI has been reported in 6% to 21% of AF patients. In addition, AMI can induce AF through inflammation and atrial diastolic overload, whereas rapid heart rate of AF leads to an increase in oxygen demand and worsening of ischaemia[11]. The question then remains on the role of SGLT2i therapy in patients who suffered AMI. Recent studies have highlighted the potential clinical benefit of SGLT2i therapy in T2D patients with AMI and a study by Chai *et al*. (2025) evaluated the efficacy and prognosis of dapagliflozin (DAPA), an SGLT2i in patients with AMI complicated by T2D. During the study, 245 patients aged 34-94 were included and the primary endpoint was defined as the composite outcome of cardiac mortality, HF events, and cerebrovascular insult stroke. The secondary endpoint was defined as death resulting from cardiac and cerebrovascular causes, excluding other factors. The results showed that primary endpoint of survival was significantly higher in the DAPA group than in the control group (P<0.05) (**Figure 1**)[13]. In addition, the overall survival rate of the DAPA group was significantly higher than the control group, the difference was statistically significant (P<0.05). These findings were suggestive that combination of DAPA with conventional anti-HF drugs is not only safe, but also effective in reducing CV adverse events, and improving long-term prognosis of patients with AMI and T2D[13]. Similarily, a systematic review and meta-analysis by Idowu *et al*. (2024) reported that SGLT2i therapy after AMI is safe and is associated with a reduced risk of HHF but not the all-cause mortality[12].

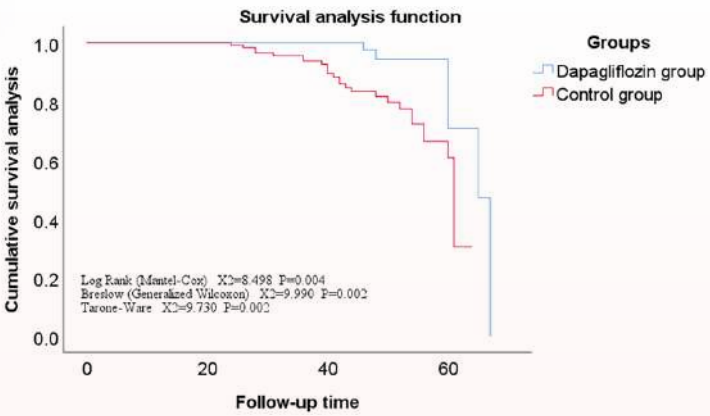


Figure 1: Survival curve of the main endpoint events in the dapagliflozin group versus the control[13]

DAPA, an SGLT2i has shown to significantly improve the overall survival among T2D patients with AMI

Bridging the Pathogenic Gap Between AMI and Aortic Valve Stenosis

Coronary artery disease is considered the root cause of AMI and is believed to frequently coexist with aortic valve stenosis (AVS)[14]. Conspicuously, AVS affects around 2-5% of the adult population aged ≥75 years, and patients with cardiac ischaemic events may experience pathological remodelling of the cardiac valves. However, the evidence linking the effects of MI to AVS has previously been poorly reported in the literature until a study by Paquin *et al*. (2022) evaluated this relationship. The study aimed to evaluate the AVS progression in patients after AMI with or without a history of MI, followed by a pathobiological evaluation of the aortic valve leaflets in animal models with MI. 68 patients with AMI, 45 with previous MI and 101 control subjects were included in the study with all three groups having comparable baseline AVS severity. Strikingly, the study found that the AMI status was significantly associated with accelerated aortic valve area progression (p=0.008)[15]. Furthermore, the aortic valve in post-MI experimental animals showed a significantly increased collagen expression compared to the control. The study concluded that AVS progression is accelerated following AMI, which is caused by increased collagen production and thickening of the aortic valve after the ischaemic events. More worryingly, these findings corroborated that patients with AVS who suffered AMI may exhibit faster valvular disease progression and may require closer follow-up[15].

Considering the burden of AMI in patients with AVS and the lack of effective treatment, Shah *et al*. (2025) evaluated the role of SGTL2i in slowing the progression of AVS in view of SGLT2is having numerous pleiotropic effects on the cardiac system. Retrospective data of 458 AVS patients on SGLT2i and 11,240 AVS patients not on SGLT2i from January 2016 to September 2022 was included in the study[16]. Surprisingly, the study found that patients on SGLT2i were less likely to have severe AVS progression (p=0.03), and the risk was progressively lower with time (<3, 6, and 12 months, respectively), as illustrated in **Figure 2**[16]. The data from the study suggested that SGTL2i may slow the progression of non-severe AVS. Arguably, patients with AMI are often understudied in SGLT2i outcome trials, and attempts should be made through large-scale randomised trials to determine efficacy and safety during early initiation, preferably within days of an AMI.

SGLT2i may slow the progression of non-severe aortic valve stenosis

Take Home Message

In summary, there is a continuing evidence gap for considering the use of SGLT2i early following AMI, and this may one day be filled and conglomerated in a holistic manner with pre-existing cardiac treatment.

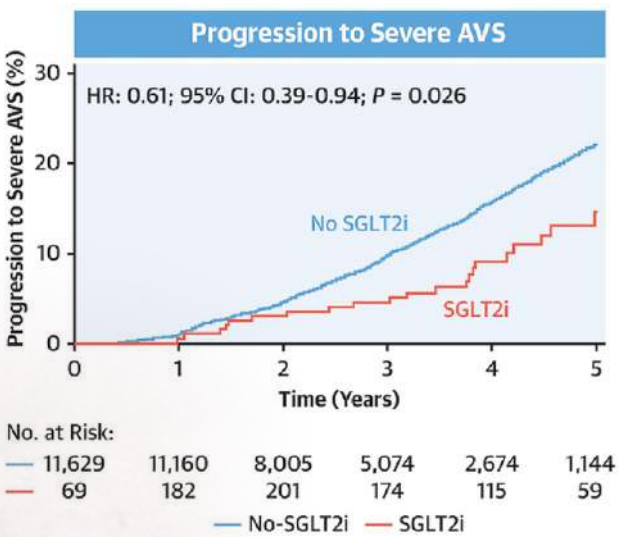


Figure 2: Progression to severe aortic stenosis with and without SGLT2 inhibitors[16]. AVS, aortic valve stenosis; CI, confidence interval; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

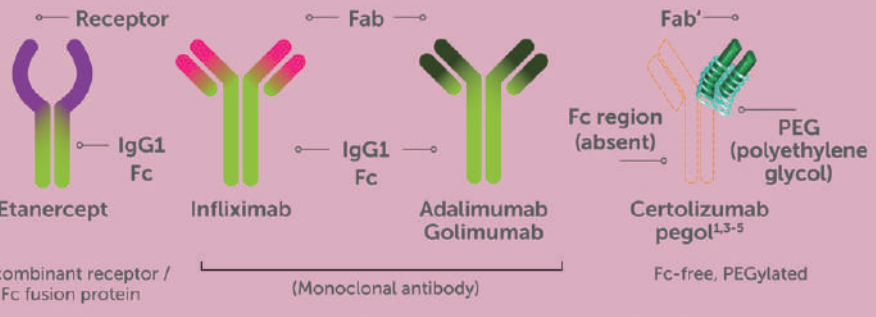
References

1. Mechanic OJ, et al. StatPearls Publishing LLC.; 2025. **2.** Ritsinger V, et al. *Eur J Prev Cardiol* 2020; 27(17): 1890-901. **3.** Zhou Y, et al. *European Heart Journal - Digital Health* 2024; 5(3): 363-70. **4.** Savarese G, et al. *Eur J Heart Fail* 2021; 23(9): 1499-511. **5.** Kocabas U, et al. *ESC Heart Fail* 2025; 12(1): 434-46. **6.** Farrero M, et al. *REC: CardioClinics* 2020; 55(1): 1-3. **7.** Kubota Y, et al. *JACC: Asia* 2022; 2(3_Part_2): 287-93. **8.** Freese Ballegaard EL, et al. *Clinical Journal of the American Society of Nephrology* 2024; 19(10). **9.** Zheng RJ, et al. *J Cardiovasc Pharmacol* 2022; 79(2): e145-e52. **10.** Zhang HD, et al. *Eur J Prev Cardiol* 2024; 31(7): 770-9. **11.** Obayashi Y, et al. *Journal of the American Heart Association* 2021; 10(18): e021417. **12.** Idowu A, et al. *Curr Probl Cardiol* 2024; 49(8): 102648. **13.** Chai J, et al. *Front Cardiovasc Med* 2025; 12: 1500978. **14.** Tomii D, et al. *Circulation* 2024; 150(25): 2046-69. **15.** Paquin A, et al. *Open Heart* 2022; 9(1). **16.** Shah T, et al. *JACC: Cardiovascular Interventions* 2025; 0(0).

WHAT IS DIFFERENT ABOUT CIMZIA®?

It is the first and only PEGylated TNF-α antagonist indicated for the treatment of active Psoriatic Arthritis & moderate to severe Plaque Psoriasis in adult patients[1,2]

Varied molecular structure of biologics[1,3-5]



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Abbreviated Hong Kong Prescribing Information

NAME OF THE MEDICINAL PRODUCT: Cimzia solution for injection in pre-filled pens (Adalimumab 200mg/1ml). Each pre-filled pen contains 200mg certolizumab pegol in 1 ml. **THERAPEUTIC INDICATIONS:** ***Rheumatoid arthritis:*** In combination with methotrexate (MTX) for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including MTX, has been inadequate. Can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. In combination with MTX, Cimzia is also indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs. ***Axial spondyloarthritis:*** Treatment of adult patients with severe active axial spondyloarthritis, comprising: Ankylosing spondylitis (AS) – Adults with severe AS who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs). Axial spondyloarthritis without radiographic evidence of AS – Adults with severe active axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to NSAIDs. ***Psoriatic arthritis:*** In combination with MTX for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. ***Plaque psoriasis:*** Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **POSOLOGY AND METHOD OF ADMINISTRATION:** ***Loading dose:*** 400mg given as 2 subcutaneous injection of 200mg each at weeks 0, 2 and 4. For the unlisted arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate. ***Maintenance dose:*** *Rheumatoid arthritis, Psoriatic arthritis:* 200mg every 2 weeks. Can consider 400mg every 4 weeks once clinical response is confirmed. MTX should be continued during treatment with Cimzia where appropriate. *Axial spondyloarthritis:* 200mg every 2 weeks or 400 mg every 4 weeks. MTX should be continued during treatment with Cimzia where appropriate. Consider reduced maintenance dose of 200mg every 4 weeks in patients with sustained remission at least 1 year after treatment. *Plaque psoriasis:* 200mg every 2 weeks. Consider 400mg every 2 weeks in patients with insufficient response. *Paediatric population (<18 years old):* No data. *Elderly (>65 years old):* No dose adjustment is required. *Renal and hepatic impairment:* No dose recommendation can be made. *Method of administration:* The total content (1 ml) of the pre-filled pen should be administered as a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis or other severe infections such as sepsis or opportunistic infections. Moderate to severe heart failure (NYHA classes IIIIV). **SPECIAL WARNINGS AND PRECAUTIONS FOR USE:** Traceability – Clearly record name and batch number of administered product. Infection (including serious infections) – Monitor closely for signs and symptoms of infections. Discontinue if patient develop serious infection or sepsis. Tuberculosis – Evaluate patients for active/inactive TB before initiating therapy. Hepatitis B Virus (HBV) reactivation – Test patients for HBV before initiating therapy. Malignancies and lymphoproliferative disorders. Skin cancers – Recommend periodic skin examination. Paediatric malignancy – Some fatal cases have been reported. Chronic obstructive pulmonary disease (COPD). Congestive heart failure – Co-administration in moderate or severe heart failure. Haematological reactions – Advise patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection. Neurological events – Carefully consider benefit/risks in patients with pre-existing or recent onset of demyelinating disorders. Hypersensitivity. Latex sensitivity. Immunosuppression. Autoimmunity. Vaccinations – Do not administer live vaccines concurrently with Cimzia. Concomitant use with other biologics. Surgery. Activated partial thromboplastin time (aPTT) assay. Elderly patients. **INTERACTIONS:** The combination of certolizumab pegol and anakinra or abatacept is not recommended. **FERTILITY, PREGNANCY AND LACTATION:** Women of childbearing potential: The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate, but the need for treatment of the woman should also be considered. Pregnancy: Cimzia administered during pregnancy could affect normal immune response in the newborn. Cimzia should only be used during pregnancy if clinically needed. Breastfeeding: Cimzia can be used during breastfeeding. Fertility: Effects on sperm motility measures and a trend of reduced sperm count in male rodents have been observed with no apparent effect on fertility. **UNDESIRABLE EFFECTS:** Bacterial infections including abscess), viral infections (including herpes, zoster, papillomavirus, influenza), eosinophilic disorders, leucopaenia (including neutropaenia, lymphopaenia), headaches (including migraine), sensory abnormalities, hypotension, nausea, hepatitis (including hepatic enzyme increased), rash (eczema, psoriasis, pain and skin), alopecia, pruritus, injection site reactions. Please refer to full prescribing information before prescribing. DATE OF REVISION OF THE TEXT: November 2021. TWHK-CZ-2400006

by Dr. Roy Lau

Anchored in Hong Kong, Connecting the Greater Bay Area - From GBA to Global Health Summit

The global healthcare industry has become an integral part of China's new-quality productive forces. Particularly, the Guangdong-Hong Kong-Macao Greater Bay Area (GBA) is emerging as a global medical hub, boasting unique strengths in research, clinical practice, services, facilities, and outstanding talent.

On 12th February 2025, the New Frontier Group, a local enterprise aiming to build the leading healthcare system that deliver world class patient care, signed a strategic cooperation agreement with the Hong Kong Investment Corporation Limited (HKIC), which is wholly owned by the Hong Kong Government for consolidating the management of the investment activities of the "Hong Kong Growth Portfolio", "Greater Bay Area Investment Fund", "Strategic Tech Fund", and the newly established "Co-Investment Fund". The parties jointly held a strategic partnership kick-off ceremony titled "Anchored in Hong Kong, Connecting the Greater Bay Area". The goal of the strategic partnership is to better utilise the leading medical research, professional medical system and efficient international networks in Hong Kong, and hence to facilitate the cross-border medical research and clinical applications.

Following the strategic partnership kick-off ceremony, the New Frontier Group hosted the first "From GBA to Global Health Summit", which was attended by over 300 domestic and international experts, scholars, and industry guests. Distinguished guest speakers, including Dr KO Wing-man, Executive Council Non-official member; Prof. Nancy IP, President of the Hong Kong University of Science and Technology; Prof. YUEN Kwok-yung, the Chair in the Department of Microbiology of the University of Hong Kong; and Prof. HE Jianxing, Director of National Respiratory Medicine Center, delivered keynote speeches and participated in panel discussions focusing on the latest developments in clinical research and treatment innovation, life sciences, the transformative role of AI in healthcare, and new trends in cross-border medical and treatment.

A Speech on cancer care by Prof. Tony Mok

The strategic partnership kick-off ceremony. (From left): Mr. Antony LEUNG, Co-founder and Chairman of New Frontier Group; Ms. Clara CHAN, CEO of HKIC; Mr. Paul CHAN, the Financial Secretary of the Hong Kong SAR Government; Mr. Carl WU, Co-founder and CEO of New Frontier Group and CEO of United Family Healthcare.

The opening speech by Ms. Clara CHAN, CEO of HKIC

Paracetamol B. Braun

Paracetamol B. Braun
10 mg/ml

Your first step in cancer pain management[1–3]

Recommended by ESMO, NCCN and WHO for cancer pain relief for adults and adolescents[1–3]

For the management of mild-to-moderate pain, in combination with an opioid[1,2]

Significantly improves pain* and well-being† in combination with stronger opioids[4]

IV paracetamol has shown to provide an opioid-sparing effect[5]

*p=0.03; †p=0.05
ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; WHO, World Health Organization

References: **1.** WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. Available at: https://www.who.int/publications/i/item/9789241550390. Accessed 22 December 2021. **2.** Fallon M, et al. *Ann Oncol* 2018;29:iv166–iv191. **3.** Swarm RA, et al. *J Natl Compr Canc Netw* 2019;17:977–1007. **4.** Stockler M, et al. *J Clin Oncol* 2004;22:3389–94. **5.** Graham GG, et al. *Inflammopharmacology* 2013;21:201–32.

Paracetamol B. Braun 10 mg/mL Solution for Infusion
Indications: • Short-term treatment of moderate pain, especially following surgery • Short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible. **Dosage and administration:** The dose to be administered and the bottle size to be used depend exclusively on the patient's weight. *50 mL bottle (restricted to toddlers and children weighing > 10 kg to ≤ 33 kg):* 15 mg/kg (1.5 mL/kg) per administration, max daily dose 60 mg/kg (not exceeding 2 g). *100 mL bottle (restricted to adults, adolescents and children weighing > 33 kg):* 15 mg/kg (1.5 mL/kg) per administration for patients > 33 kg to ≤ 50 kg, max daily dose 60 mg/kg (not exceeding 3 g); 1 g (100 mL) per administration for patients > 50 kg with no additional risk factors for hepatotoxicity, max daily dose 4 g; 1 g (100 mL) per administration for patients > 50 kg with additional risk factors for hepatotoxicity, max daily dose 3 g. The max daily dose should be adjusted accordingly taking the administration of other paracetamol-containing products into account. No more than 4 doses to be given in 24 hours. Administration: The paracetamol solution is administered as a 15-minute IV infusion. The minimum interval between each administration must be at least 4 hours, and at least 6 hours in patients with severe renal insufficiency. The product can be diluted in a 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution or a combination of both solutions up to one tenth (one volume Paracetamol B. Braun into nine volumes diluent). In this case, use the diluted solution within the hour following its preparation (infusion time included). For single use only. **Contraindication:** • Hypersensitivity to paracetamol, propacetamol hydrochloride (prodrug of paracetamol) or to any of the excipients (Mannitol, Sodium citrate dihydrate, Acetic acid glacial and Water for injections). • Cases of severe hepatocellular insufficiency. **Special precautions:** Risk of medication errors due to confusion between mg and mL. Prolonged or frequent use is discouraged. May require dose adjustment if other medicines administered contain either paracetamol or propacetamol. Doses higher than those recommended entail the risk of very serious liver damage. Use with caution in cases of: • Hepatocellular insufficiency • Severe renal insufficiency (Creatinine clearance ≤ 30 mL/min) • Chronic alcoholism • Chronic malnutrition (low reserves of hepatic glutathione) • Dehydration • Genetically caused G-6-PD deficiency (haemolytic anaemia possible). Contains less than 1 mmol sodium (23 mg) per container, i.e. essentially 'sodium-free'. **Interactions:** Probenecid. Salicylamide. Enzyme-inducing substances. Oral anticoagulants, when paracetamol is dosed 4 g per day for ≥ 4 days. **Adverse reactions:** *Frequent:* Adverse reactions at injection site (pain and burning sensation). *Rare:* Malaise, increased levels of hepatic transaminases, hypotension. *Very rare:* Thrombocytopenia, leucopenia, neutropenia, hypersensitivity reaction, serious skin reactions. *Frequency not known:* Pruritus, erythema, flushing, tachycardia. **Presentation:** 50 mL bottle containing 500 mg paracetamol; 100 mL bottle containing 1,000 mg paracetamol.
Refer to full packaging leaflet for complete information. Ref: 04/2019

Please refer to full prescribing information before prescribing.

HC021/Para/21/DEC

B. Braun Medical (H.K.) Ltd.
Unit Nos. 13–18, Level 35, Tower 1, Millennium City 1, No. 388 Kwun Tong Road, Kwun Tong, Hong Kong
Tel: (852) 2277 6100 | Fax: (852) 2865 6095 | www.bbraun.com

B BRAUN
SHARING EXPERTISE

by Michelle Lee

Transforming Diabetes Outcomes: The Clinical Power of Insulin Glargine U300

Organised by:

香港糖尿科護士協會
Association of Hong Kong Diabetes Nurses

Moderator:

Prof. Juliana Chan

- Professor of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong (CUHK), Hong Kong

Speakers:

Prof. Didac Mauricio

- Professor of Medicine, Faculty of Medicine, University of Vic & Central University of Catalonia (UVic/UCC), Barcelona, Spain

Dr. Peter Chun-Yip Tong

- Specialist in Endocrinology, Diabetes & Metabolism

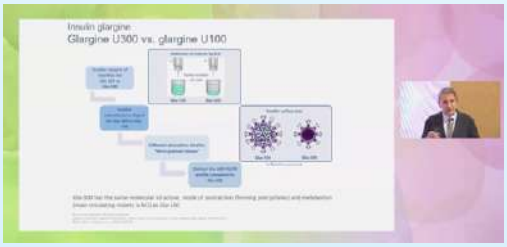
Prof. Elaine Chow

- Associate Professor, Faculty of Medicine, CUHK

Diabetes mellitus (DM) remains a global health challenge, with insulin therapy playing a pivotal role in managing the condition. Insulin glargine U300 (Gla-300), a second-generation basal insulin analogues has emerged as a transformative treatment option, offering an improved glycaemic control and reduced hypoglycaemia risk among patients with DM compared to earlier insulin formulations.

On 4th March 2025, world-renowned healthcare experts in Endocrinology gathered at the Regency Ballroom, Hyatt Regency, Hong Kong, organised by the Association of Hong Kong Diabetes Nurses (AHKDN) and the Diabetes Hongkong (DHK) for an insightful professional symposium on the clinical and practical aspects of Gla-300. Prof. Juliana Chan, a professor of Medicine at the CHUK made an opening remark emphasising the importance of insulin in diabetes management This was then followed by one of the key speakers, Prof. Didac Mauricio, a world-renowned endocrine specialist from the UVic/UCC who delivered a comprehensive presentation titled "Transforming Diabetes Outcomes: The Clinical Power of Insulin Glargine U300". He emphasised the robust clinical evidence supporting the efficacy and safety of Gla-300, and its role in improving patient outcomes. Next, Dr. Peter CY Tong, a specialist in Endocrinology, Diabetes & Metabolism, shared his practical insights on the initiation, titration and persistence of Gla-300. This was followed by Prof. Elaine Chow, who presented her findings on transitioning patients from neutral protamine Hagedorn (NPH) insulin to Gla-300 and the compelling data on the benefits of using Gla-300 clinically.

Following the presentations, an interactive Q&A and panel discussion ensued on the real-world application of Gla-300 and the benefit of basal insulin analogous over NPH. Finally, the symposium concluded with a closing remark by Prof. Chan that reiterated the importance of leveraging advanced therapies like Gla-300 to elevate diabetes care standards.



by Dr. Mohsin Roshan

Practical Information on the Use of a Modern Haemostatic Matrix in Urology from the Perspective of a Urological Surgeon

Organised by:

香港泌尿外科學會
Hong Kong Urological Association

Moderator:

Dr. Yun Sang Chan, Samson

- *Consultant Urologist, Tuen Mun Hospital, Hong Kong (H.K.)*
- *Member of Urology Specialty Group, Central Coordinating Committee (COC) (Surgery) & the Surgical Outcomes Monitoring & Improvement Programme (SOMIP) Steering Committee*

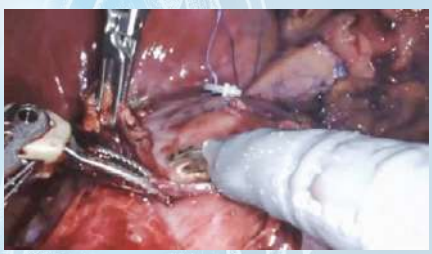
Speakers:

Professor Marcin Słojewski

Head of Department of Urology and Urological Oncology, University Hospital No 2, Pomeranian Medical University, Szczecin, Poland

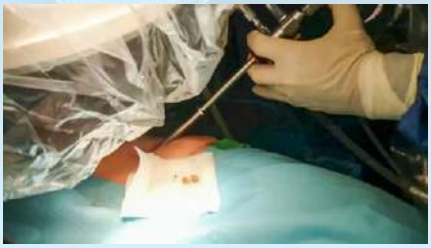
There has been a recent and near exponential increase in the use of haemostatic agents and sealants to supplement the rapidly evolving methods in the surgical management of urological patients. To understand the role of the modern haemostatic matrix in the field of Urology, a symposium organised by the Hong Kong Urological Association (HKUA) invited Professor Marcin Słojewski, a renowned Professor in Urology to share his expertise. Prof. Słojewski briefly introduced his role as a surgeon in Szczecin and the evolution of surgery from open surgery to robotic surgery. This was then followed by a brief discussion on bleeding prevention techniques used intraoperatively and the importance of haemodynamic monitoring both intra- and postoperatively. Prof. Słojewski then highlighted the practical application of fibrin sealant patch in Urological surgeries, which included tubeless percutaneous nephrolithotomy (PCNL), robotic partial nephrectomy, and robotic radical prostatectomy. He reiterated that clinical benefits of medicated sponge with human thrombin and human fibrinogen in Urology include enhanced haemostasis, shorter hospital stay, and lower incidence of urine leakage. His final remarks for the symposium was that medicated sponge with human thrombin and human fibrinogen is efficacious and a valuable tool for improving surgical outcomes, in addition to the patient safety.

Dr. Chan made an opening remark introducing Prof. Słojewski



Application of medicated sponge with human thrombin & human fibrinogen in robotic partial nephrectomy

Prof. Słojewski discussed ways to overcome bleeding risk in urological procedures



Application of medicated sponge with human thrombin & human fibrinogen in PCNL

by Migee Tang

On-the-Pulse

Neurology

Cognitive Landscapes – Environmental Pathways to Dementia[1]

Dementia affects millions of individuals globally, and prevention remains paramount. A recent systematic review which evaluated the relationship between environmental factors and cognitive decline revealed air pollutants, including particulate matters and nitrogen oxides, increase the risk of dementia, in addition to accelerating cognitive decline[1]. Notably, individuals living near enhanced walkable and accessible local amenities showed better cognitive health compared to those who lived near major roads. These findings underscore the correlation between the environment and dementia risk, as well as the importance of designing an urbanized living that promotes cognitive well-being of individuals.

Pediatrics

TGFβ: A Key Player in Pediatric COVID-19 Complications[2,3]

While children were observed to experience less severe symptoms of Coronavirus 2019 (COVID-19) than adults, SARS-CoV-2 infection can lead to a severe hyperinflammatory condition known as multisystem inflammatory syndrome in children (MIS-C), which typically occurs 4-8 weeks post-infection[2]. MIS-C is marked by specific T cell expansion and systemic hyperinflammation, yet its underlying mechanisms remained largely unclear. A recent study reveals that acute MIS-C is associated with impaired reactivation of virus-reactive memory T cells, which is linked to elevated serum levels of the cytokine transforming growth factor β (TGFβ)[3]. This impairment leads to functional changes in T cells, B cells, and monocytes, which can potentially be reversed by blocking TGFβ. Moreover, signs of Epstein-Barr virus (EBV) reactivation have been observed in MIS-C patients, whose immune systems are hindered by TGFβ to suppress EBV, leading to hyperinflammation. This study highlights the complex role TGFβ plays in driving inflammation and suggests TGFβ as a promising treatment target for MIS-C as well as other COVID-related complications.

Infectious Disease

Viral Currents – A Quick Look at Norovirus[4]

As Hong Kong transitions into a humid Spring, norovirus, which has remained the leading cause of acute gastroenteritis (AGE) globally, also proliferates[4]. Noroviruses are transmitted via the fecal-oral route and a small number of virions are sufficient to cause infection, making outbreaks difficult to control. Symptoms caused by norovirus are often mild and typically resolve after 2-3 days. Nonetheless, prevention of norovirus infections remains challenging due to its genetic diversity. Interestingly, this may be about to change with ongoing efforts to develop messenger ribonucleic acid (mRNA) based vaccines and adenovirus vectors in both adults and pediatric populations[4]. Notably, the key to norovirus prevention remains good hand hygiene, which curbs its spread and resilience in the community.

"Fostering Innovation Through Continuous Medical Education with On the Pulse"

References

1. Da L, et al. Ageing Research Reviews 2025;104:102630. **2.** Okuducu YK, et al. Clin. Chest Med 2024;45:675–684. **3.** Goetzke CC, et al. Nature 2025. https://doi.org/10.1038/s41586-025-08697-6. **4.** Carlson KB, et al. NPJ Vaccines 2024;9(1):94.

Medical Oncology:

LOTUSENZA®

(letrozole)

LOTUS

HK Reg. No. HK68544 (16 Jan, 2025)

Composition[1]:

- Yellow, circular, biconvex film-coated tablets, plain on both sides
- Each tablet contains 2.5 mg letrozole

Indication[1]:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer
- Extended adjuvant treatment of hormone-dependent early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy for 5 years
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer
- Advanced breast cancer after relapse or disease progression, in women with natural or artificially induced postmenopausal endocrine status, who have previously been treated with antiestrogens
- Neoadjuvant treatment of postmenopausal women with hormone receptor positive, HER-2 negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated

Respiratory Vaccination:

PnuPreve 23

(pneumococcal vaccines)

SINOVAC

HK Reg. No. HK68548 (17 Jan, 2025)

Composition[2]:

- 23-valent pneumococcal polysaccharide vaccine
- Covering serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F

Indication[2]:

- To prevent pneumococcal diseases in adults and children aged 2 years and above

Respiratory Oncology:

IMDELLTRA®

(drug powder vial: tarlatamab; stabilizer solution vial: stabilizer solution)

AMGEN

HK Reg. No. HK-68549, HK-68550 (17 Jan, 2025)

Composition[3]:

- For injection: 1 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution
- For injection: 10 mg of lyophilized powder in a single-dose vial for reconstitution and further dilution

Indication[3*]:

- Imdelltra is indicated for the treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy*

** This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)[3]*

Intensive Care:

NOTRIXUM®

(atracurium besilate)

HONG KONG MEDICAL SUPPLIES LTD

HK Reg. No. HK68565, HK68566 (11 Feb, 2025)

Composition[4]:

- One ampoule with 2.5 ml solution contains 25 mg atracurium besilate
- One ampoule with 5 ml solution contains 50 mg atracurium besilate

Indication[4]:

- Notrixum is used as an adjunct to general anesthesia or sedation in the intensive care unit (ICU), to relax skeletal muscles, and to facilitate tracheal intubation and mechanical ventilation

References

1. EMC. Letrozole 2.5 mg film-coated tablets SmPC. 30 December 2024. Available from: https://www.medicines.org.uk/emc/product/9957/smpc#gref. [Accessed 19 February 2025]. **2.** Sinovac. 23-Valent Pneumococcal Polysaccharide Vaccine. Available from: https://www.sinovac.com/zh-cn/portfolio/ppv23. [Accessed 20 February 2025]. **3.** FDA. IMDELLTRA® Highlights of Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761344s000lbl.pdf. [Accessed 20 February 2025]. **4.** EMC. Atracurium besilate SmPC. 2 November 2023. Available from: https://www.medicines.org.uk/emc/product/951/smpc#gref. [Accessed 20 February 2025].

Keep Up With the Pace of Drug Development Evolution and Discover the Newly Launched Treatment in Hong Kong

ORGANON
Here for her health

Atozet®
(ezetimibe and atorvastatin) tablets

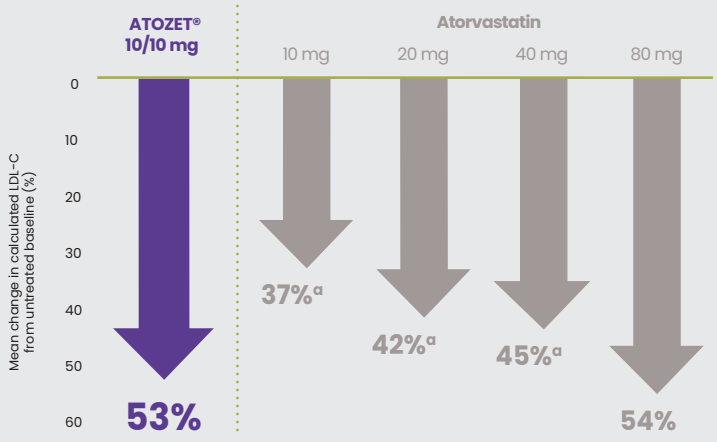
POWERFUL LDL-C REDUCTION WITH ATOZET®

in high risk/very high risk patients with dyslipidemia[1]

In a clinical study of patients with hyperlipidemia and not on lipid-lowering therapy,

ATOZET® (Ezetimibe/ Atorvastatin) 10/10 mg powerfully lowered mean LDL-C by 53%[1]

Efficacy of the lowest dose of ATOZET® (10/10 mg) was similar to that the highest dose of Atorvastatin (80 mg)[1]



Mean pooled untreated baseline calculated LDL-C was 4.70 mmol/L (n=255) for the group receiving ATOZET® and 4.69 mmol/L (n=248) for the group receiving Atorvastatin. Mean reduction in calculated LDL-C from untreated baseline was 54% for ATOZET® 10/20 mg; 56% for ATOZET® 10/40 mg* and 61% for ATOZET® 10/80 mg*.[1]
* Strengths not available in some countries
[a] $p<0.01$ for combination therapy vs. corresponding dose of atorvastatin alone

Study design: In a prospective, randomized, double-blind study, 628 patients with baseline LDL-C 145 to 250 mg/dL and triglycerides ≤350 mg/dL were randomly assigned to receive 1 of the following for 12 weeks: ezetimibe (10 mg/d); atorvastatin (10, 20, 40, or 80 mg/d); ezetimibe (10 mg) plus atorvastatin (10, 20, 40, or 80 mg/d); or placebo. The primary efficacy end point was percentage reduction in LDL-C for pooled ezetimibe plus atorvastatin versus pooled atorvastatin treatment groups.

Reference

1. Ballantyne, C. M. et al. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolemia - A Prospective, Randomized, Double-Blind Trial. Circulation. 107,2409–2415 (2003).

ATOZET® Selected Safety Information

INDICATIONS: Prevention of Cardiovascular Events ATOZET is indicated to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. Hypercholesterolaemia ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate • patients not appropriately controlled with a statin alone • patients already treated with a statin and ezetimibe Homozygous Familial Hypercholesterolaemia (HoFH) ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis). **Contraindications:** • Hypersensitivity to the active substances or to any of the excipients. • Therapy with ATOZET is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures. • ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN). • ATOZET is contraindicated in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir. **Precautions:** • Myopathy/Rhabdomyolysis » In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. Most patients who developed rhabdomyolysis were taking a statin concomitantly with ezetimibe. Rhabdomyolysis has been reported very rarely with ezetimibe monotherapy. » Also, ATOZET contains atorvastatin, which is a HMG-CoA reductase inhibitor. Atorvastatin may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis. » A CPK level should be measured before starting treatment. If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started. » Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET • Liver Enzymes » Liver function tests should be performed before the initiation of treatment and periodically thereafter. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended. • Hepatic Insufficiency » Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ATOZET is not recommended. • Interstitial lung disease » If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued. • Diabetes mellitus » Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI>30kg/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines. • Excipients » ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine. **Adverse events:** • Common adverse reactions (≥1/100, <1/10) include diarrhoea and myalgia. • In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy. • Please consult the full prescribing information for detailed adverse events. Before prescribing, please consult the full prescribing information.
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SC-NON-110153 Jan/2024

SIMPLE AS THAT!

HAVE CONFIDENCE IN CONSISTENT CHC CURE WITH **EPCLUSA®** FOR TODAY'S PATIENT ENVIRONMENT[1]

Epclusa® is proved suitable for a minimal monitoring approach (MINMON):[2]

- **No pre-treatment genotyping**
- **Full course of treatment dispensed at the first visit**
- **No laboratory monitoring**
- **Remote contacts** (Final assessment at week 24)

CHC: Chronic Hepatitis C

Product photo shown is not actual size.

Reference:

1. Epclusa Prescribing Information. (Version: HK-APR22-EU-MAR21-ICGPS-AUG20).
2. Solomon SS, Wagner-Cardoso S, Smeaton L, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2022;7(4):307-317.

EPCLUSA® Abbreviated Prescribing Information (Version: HK-APR22-EU-MAR21-ICGPS-AUG20) **Presentation:** Pink, diamond-shaped, film-coated tablet of dimensions 20 mm x 10 mm, debossed on one side with "GSI" and "7916" on the other side. **Indications:** Epclusa is indicated for the treatment of chronic hepatitis C virus (HCV) infection in patients aged 12 years and older and weighing at least 30 kg. **Dosage:** Adults: one tablet, taken orally, once daily with or without food for 12 weeks. Patients aged 12 to < 18 years and weighing at least 30 kg: one tablet, taken orally, once daily with or without food for 12 weeks. Adult patients who have previously failed therapy with an NS5A-containing regimen: Epclusa with ribavirin for 24 weeks may be considered. Elderly: No dose adjustment is warranted for elderly patients. Renal impairment: Epclusa can be used in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) and end stage renal disease (ESRD) requiring haemodialysis with no dose adjustment. Hepatic impairment: No dose adjustment of Epclusa is required for patients with mild, moderate, or severe hepatic impairment (CPT Class A, B, or C). Safety and efficacy of Epclusa have been assessed in patients with CPT Class B cirrhosis, but not in patients with CPT Class C cirrhosis. Paediatric population: The safety and efficacy of Epclusa in children aged less than 12 years or weighing less than 30 kg have not yet been established. **Contraindications:** Hypersensitivity to the active substances or to any of the excipients. Medicinal products that are strong P-glycoprotein (P-gp) or strong cytochrome P450 (CYP) inducers (carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin and St. John's wort). **Warnings and Precautions:** Epclusa should not be administered concurrently with other medicinal products containing sofosbuvir. Severe bradycardia and heart block: Life-threatening cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone. Amiodarone should only be used in patients on Epclusa when other alternative anti-arrhythmic treatments are not tolerated or are contraindicated. Patients should undergo cardiac monitoring in an in-patient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Monitoring should also be carried out for patients who have discontinued amiodarone within the past few months and are to be initiated on Epclusa. All patients with concurrent or recent use of amiodarone should be warned of the symptoms of bradycardia and heart block and should be advised to seek medical advice urgently should they experience them. HCV/HBV (hepatitis B virus) co-infection: Cases of HBV reactivation, some of them fatal, have been reported during or after treatment with direct-acting antiviral agents. HBV screening should be performed in all patients before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored and managed according to current clinical guidelines. Patients who have previously failed therapy with an NS5A-containing regimen: There are no clinical data to support the efficacy of sofosbuvir/velpatasvir for the treatment of patients who have failed treatment with a regimen containing another NS5A inhibitor. Treatment with Epclusa + RBV for 24 weeks can be considered for patients who have failed therapy on an NS5A-containing regimen and who are deemed at high risk for clinical disease progression and who do not have alternative treatment options. Renal impairment: Safety data are limited in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) and ESRD requiring haemodialysis. Epclusa can be used in these patients with no dose adjustment when no other relevant treatment options are available. Use with moderate P-gp inducers or moderate CYP inducers: Co-administration of such medicinal products that are moderate P-gp or moderate CYP inducers (e.g. efavirenz, modafinil, oxcarbazepine or rifapentine) with Epclusa is not recommended. Use with certain HIV antiretroviral regimens: Patients receiving Epclusa concomitantly with elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for tenofovir-associated adverse reactions. Use in diabetic patients: Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. Glucose levels of diabetic patients initiating direct-acting antiviral therapy should be closely monitored, particularly within the first 3 months, and their diabetic medication modified when necessary. The physician in charge of the diabetic care of the patient should be informed when direct-acting antiviral therapy is initiated. CPT Class C cirrhosis: Safety and efficacy of Epclusa has not been assessed in patients with CPT Class C cirrhosis. Liver transplant patients: The safety and efficacy of Epclusa in the treatment of HCV infection in patients who are post-liver transplant have not been assessed. **Adverse reactions:** Common adverse drug reactions include rash. Cases of severe bradycardia and heart block have been observed when sofosbuvir-containing regimens are used in combination with amiodarone and/or other medicinal products that lower heart rate. Steven-Johnson syndrome with unknown frequency. **Drug interactions:** Patients treated with vitamin K antagonists: As liver function may change during treatment with Epclusa, a close monitoring of International Normalised Ratio (INR) values is recommended. Impact of DAA therapy on drugs metabolized by the liver: The pharmacokinetics of drugs that are metabolized by the liver (e.g. immunosuppressive agents such as calcineurin inhibitors) may be impacted by changes in liver function during DAA therapy, related to clearance of HCV. Interactions between Epclusa and other medicinal products: Acid reducing agents including antacids (aluminium, magnesium hydroxide, calcium carbonate), H2-receptor antagonists (famotidine, cimetidine, nizatidine, ranitidine), proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole); Antiarrhythmics such as amiodarone, digoxin; Anticoagulants such as dabigatran etexilate and Vitamin K antagonists; Anticonvulsants such as carbamazepine, phenytoin, phenobarbital and oxcarbazepine; Antimycobacterials such as rifampicin, rifabutin and rifapentine; HIV antiviral agents: reverse transcriptase inhibitors such as tenofovir disoproxil fumarate, efavirenz/ emtricitabine/ tenofovir disoproxil fumarate; Herbal supplements such as St. John's wort; HMG-CoA reductase inhibitors such as rosuvastatin, and other statins. Immunosuppressants such as ciclosporin and tacrolimus.

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

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