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Uncovering the Art of Perfect Matching – A Review on Precision Oncology

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A New Treatment Era with Daratumumab in Transplant-eligible Newly Diagnosed MM Patients

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References: 1. Toujeo® Hong Kong prescribing information. 2020 ver 1. 2. Yki-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.
Legal Classification: Part 1 Poison **Full prescribing information is available upon request.**
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Dear Reader,

Precision oncology (PO) has revolutionised the landscape of cancer treatments, which has shifted away from non-specific cytotoxic treatment to a more individualised manner. Facilitated by the advancement in diagnostic technologies, particularly next-generation sequencing (NGS), PO optimises cancer treatment outcomes by improving the matching between patients and therapies. However, there are practical obstacles, such as accuracy, policy, and cost, hindering the clinical applications of PO approach. Fortunately, emerging techniques, including artificial intelligence (AI), have been implemented to enhance the clinical performance of PO. The technical basis, clinical performance, and future development of PO approach in cancer management will be discussed in the Feature Story.

In the Focus section, clinical issues concerning influenza in children will be discussed. Remarkably, children are at high risk of influenza infection due to immature immune system, whereas approximately 10% of seasonal influenza infections occur in children under the age of 5, with around 870,000 annual hospitalisations. While vaccination is recommended in most countries, some reports reflected that some parents perceived that their child was not at risk for influenza or severe illness from influenza. This was the most common reason for not vaccinating children.

In addition to the thematic topics, updates on pharmacologic management of viral hepatitis, relapsed/refractory multiple myeloma (RRMM), and epilepsy are featured in the Industry Updates. Interestingly, the relationship between diabetes mellitus (DM) and dark chocolate consumption will be explored in the Epoch section.

Hope you enjoy this issue!

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

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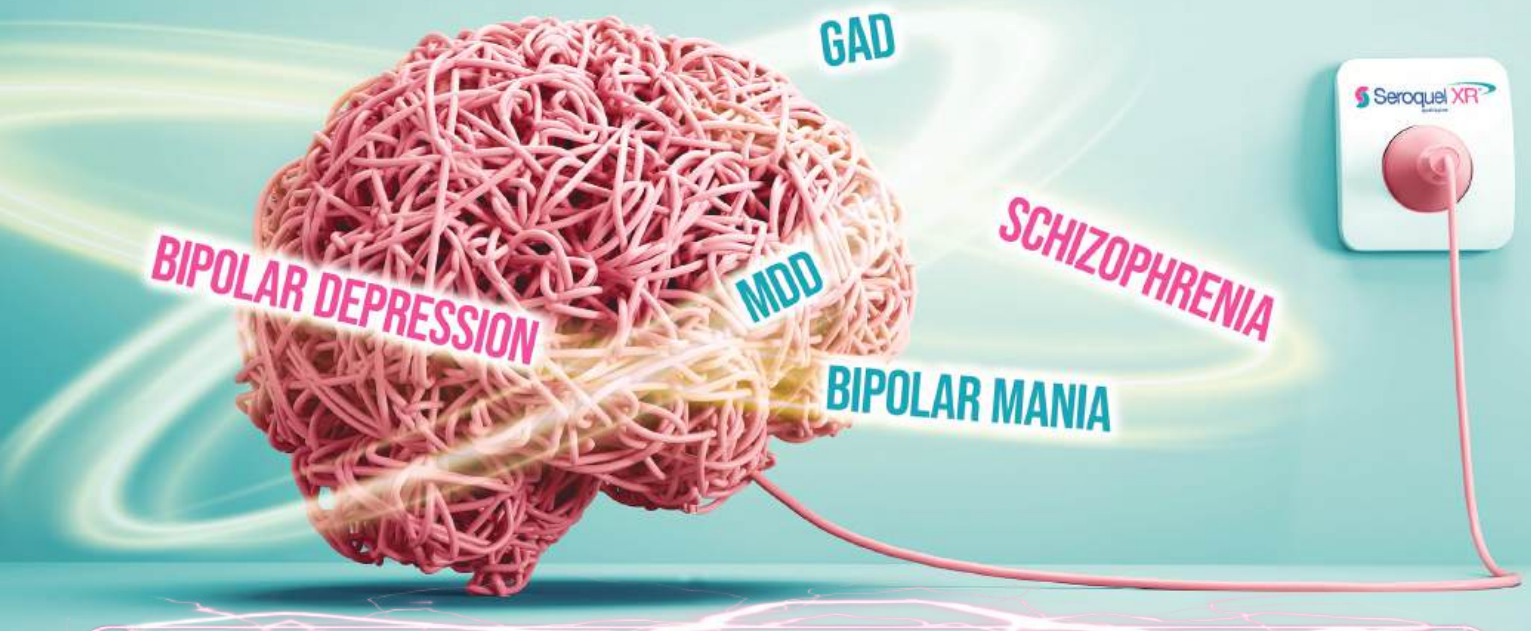

APPROVED INDICATIONS

- Bipolar Depression - 50-600mg/day*
- Major Depressive Disorder (MDD) - 50-300mg/day*
- Schizophrenia - 400-800mg/day*
- Bipolar Mania - 400-800mg/day*
- Generalised Anxiety Disorder (GAD) - 50-150mg/day*

* Dose range for acute treatment

Abbreviated Prescribing Information: Presentation: Quetiapine fumarate extended-release tablet. Indications: Bipolar Disorder: Maintenance treatment of bipolar I disorder; as monotherapy or in combination with lithium or sodium valproate, for prevention of relapse/recurrence of manic, depressive or mixed episodes; Treatment of depressive episodes associated with bipolar disorder; Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate. Schizophrenia: Treatment of schizophrenia, prevention of relapse and maintenance of clinical improvement during continuation therapy. Major Depressive Disorder (MDD): Treatment of recurrent MDD in patients who are intolerant of, or who have an inadequate response to alternative therapies. Generalised Anxiety Disorder (GAD): Treatment of GAD. Dosage: Once daily, without food. Bipolar Disorder: Maintenance treatment: Use same dose as active treatment for prevention of manic, depressive or mixed episodes in bipolar disorder. Range 300-800 mg/day. Bipolar Depression: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4). Can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8. Acute Mania: 300 mg (Day 1), 600 mg (Day 2), up to 800 mg (after Day 2), alone or in combination with a mood stabilizer. Range 400-800 mg/day. Schizophrenia: 300 mg (Day 1), 600 mg (Day 2) and up to 800 mg after Day 2. Range 400-800 mg/day depending on response and tolerability. Same dosage for maintenance therapy. Recurrent MDD: Once daily in the evening. 50 mg (Day 1 & 2), increased to 150 mg on Day 3 & 4. Usual effective dosage: 150 mg. Range of 50-300 mg/day. Same dosage for maintenance therapy. GAD: 50 mg (Day 1 & 2), 150 mg (Day 3 & 4). Range 50-150 mg/day. Switching from Seroquel immediately release: Switch at equivalent total daily dose. Individual adjustments may be necessary. Elderly: 50 mg/day, increased in increments of 50 mg/day up to an effective dose depending on response and tolerability. Slower dose titration is recommended. Elderly MDD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg (Day 8), up to 300 mg depending on response and tolerability. Elderly GAD: 50 mg (Day 1-3), 100 mg (Day 4), 150 mg on Day 8. Patients with renal impairment: No dosage adjustment needed. Patients with hepatic impairment: 50 mg/day up to an effective dose. Contraindications: Hypersensitive to any components of this product. Precautions: Elderly patients with dementia-related psychosis or behavioural disorders; rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption; concomitant use with ADHD medication; conditions predisposing to hypotension; family history of QT prolongation, congenital long QT syndrome, heart failure, hypokalaemia or hypomagnesaemia, concomitant medicines known to prolong QTc interval; history of seizures, conditions that potentially lower seizure threshold; elevation in core body temperature; risk for spiration pneumonia. Interactions: Centrally acting drugs: thioridazine; lorazepam; levodopa and dopamine agonists.CYP3A4 inhibitors: azole antifungals; macrolide antibiotics; protease inhibitors; grapefruit juice. Hepatic enzyme inducers: carbamazepine; phenytoin. Undesirable effects: Sedation; somnolence; insomnia; dizziness; syncope; headache; increased appetite; weight gain; dysphagia; dry mouth; nausea & vomiting; constipation; dyspepsia; tachycardia; palpitations; orthostatic hypotension; rhinitis; dyspnoea; blurred vision; abnormal dreams & nightmares; asthenia; dysarthria; fatigue; myalgia; peripheral edema; irritability; pyrexia; lipid changes; worsening of metabolic factors; elevations in serum transaminases (ALT, AST), γ-GT & serum prolactin; increases eosinophils: decreases in total T4, free T4 & total T3, and increases in TSH; leucopenia and/or neutropenia; mild asthenia; withdrawal symptoms after abrupt cessation. Full local prescribing information is available upon request.

Please read the complete prescribing information before prescribing.

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by Dr. Roy Lau

Oncology

Uncovering the Art of Perfect Matching – A Review on Precision Oncology

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Precision oncology (PO), defined as molecular profiling of tumours to identify targetable alteration[1]. The approach has shifted away from non-specific cytotoxic treatment to a more individualised cancer treatment. The advancement in diagnostic technologies, such as next-generation sequencing (NGS), with decision support applications and the availability of patient databases has facilitated optimal cancer management. While PO has proven successful in improving patient outcomes and quality of life (QoL), challenges still persist due to hinderance its use for matching therapies to the patients. Fortunately, emerging techniques, including artificial intelligence (AI), have been implemented to enhance the clinical performance of PO. This review aimed to outline some of the practical issues related to PO and its recent development.

Precision Oncology – What and Why?

PO involves the detection of tumour-specific aberrations and combating them with drugs that targets cells with the altered genomic status[2]. In fact, the concept of PO is not new since the *BCR-ABL* rearrangement in chronic myeloid leukaemia (CML) was identified and targeted by imatinib in 1998, which led to dramatic clinical remissions. Accordingly, the therapy was approved by the U.S. Food and Drug Administration (FDA) in 2001[1].

With the development of sophisticated "omic" methods, profiling of the complex molecular characteristics of tumours, such as DNA sequence data (genomics), RNA analysis (transcriptomics), protein levels (proteomics), cellular metabolism (metabolomics), etc, has become readily available[3]. The discovery of actionable mutations and biomarker profiling not only improves our understanding of cancer biology but also helps to optimise clinical management of oncology patients.

Analysis of nationwide database in the United States (U.S.) by Steuten *et al*. (2019) involving 5,688 patients with advanced non–small-cell lung cancer (NSCLC), who received multigene panel sequencing (MGPS, n=875) or single-marker genetic testing (SMGT, n=4,813), revealed that 30.1% of MGPS-tested patients had evidence of an actionable mutation, such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), and 21.4% received a targeted treatment, whereas actionable mutation was found in 23.3% of SMGT-tested patients and 18.7% received a targeted treatment (**Figure 1**). Essentially, the results suggested that patients who received targeted treatments for specific mutations exhibited better overall survival (OS) compared to those who did not receive a targeted treatment (mean adjusted OS: 2.31 years [targeted treatment] vs 1.73 years [non-targeted treatment])[4].

Therefore, using biomarker profiling to guide cancer treatment likely improves the therapeutic outcomes

for cancer patients. Remarkably, the advent of NGS on formalin-fixed, paraffin-embedded tissues allows the determination of mutations in a large number of genes in a timely and cost-effective manner.

Next-generation Sequencing Drives the Clinical Applications of Precision Oncology

NGS is a technology for deoxyribonucleic acid/ribonucleic acid (DNA/RNA) sequencing and mutation detection. Practically, the major steps involved in NGS include DNA/RNA fragmentation, library preparation, massive parallel sequencing, bioinformatics analysis, and mutation annotation and interpretation (**Figure 2**)[5]. Briefly, DNA fragmentation is the process of breaking down targeted DNA into segments of 100-300 base pair (bp) in length. Relevant segments are then extracted by hybridisation capture assay or polymerase chain reaction (PCR) amplification. Library preparation is a process by which DNA segments are modified so that each DNA sample can have a sample-specific index. It also allows the sequencing adaptors to be added to the DNA segments. The DNA segments are then proceeded to massive parallel sequencing using an NGS sequencer. Subsequently, the sequence information generated from massive parallel sequencing is analysed using bioinformatics software[6].

NGS enables the rapid, cost-effective detection of a broad spectrum of well-characterised genomic alterations, including short structural variants (SSVs), copy number alterations (CNAs), translocations, and fusions in multiple genes. The technology drives the clinical application of PO due to the rapid expansion of treatable gene aberrations and predictive biomarkers in recent years, especially in lung cancer and gynaecological oncology. For instance, the recent data from the United Kingdom (U.K.) 100,000 Genomes Project provided whole-genome sequencing information for 13,880 solid tumours. Interestingly, the findings revealed clinically relevant mutations were present in 20-49% of gynaecological cancers, including invasive breast carcinoma, high-grade ovarian serous carcinoma, and uterine endometrial carcinoma[7]. Hence, large-scale tumour molecular profiling programs using NGS have fostered the growth of precision cancer

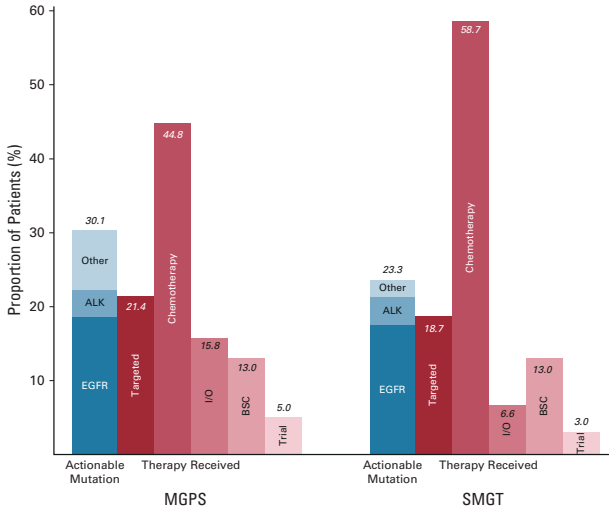

Figure 1. *The proportion of patients with an actionable mutation and type of therapy received*[4]

medicine, while NGS-based molecular pathology has become an essential tool in driving therapeutic decision-making.

Clinical Benefits of Matching the Right Therapy with the Right Patient

The advent of PO has changed the landscape of oncologic biomarkers, drug discovery, and outcomes for patients with cancer. For most cancer types, the one-size-fits-all treatment approach is fast becoming obsolete, whereas the PO approach, which treats the right patient with the right treatment at the right time, has rapidly entered mainstream clinical practice. The PO approach to cancer treatment aims to maximise clinical efficacy, minimise safety concerns, and reduce economic burden.

While NGS cancer profiling has gained traction in routine clinical practice in South Korea, a recent analysis of real-world data of 990 patients with advanced solid tumours in tertiary hospitals by Kim *et al*. (2025) evaluated the outcomes of NGS testing and genomically matched therapies. Among patients with variants of strong clinical significance such as FDA-approved, professional guidelines, or well-powered research-based therapy (tier I variants), the most frequently altered genes detected were Kirsten rat sarcoma virus (KRAS) (10.7%), followed by EGFR (2.7%) and V-Raf Murine

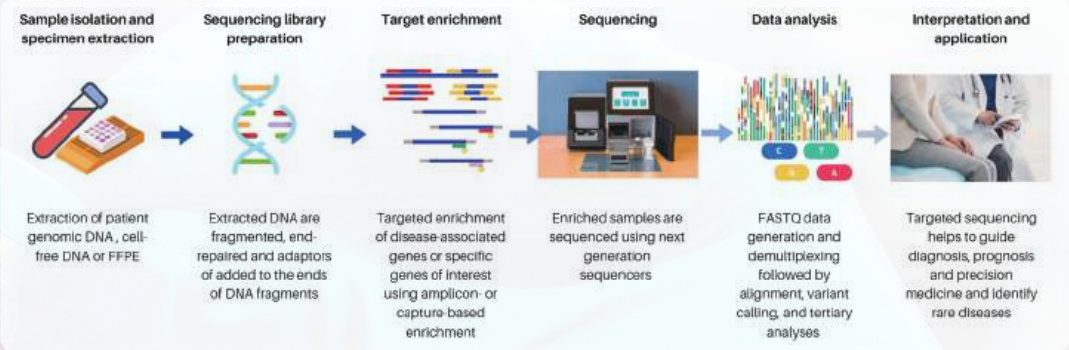

Figure 2. *General workflow of NGS*[5]

Sarcoma Viral Oncogene Homolog B (BRAF) (1.7%, **Figure 3**). Among patients with measurable lesions who received NGS-based therapy (n=32), 37.5% achieved a partial response, and 34.4% achieved the stable disease. The results further suggested that NGS-based therapy resulted in a higher response rate (37.5%) than standard of care. The median treatment duration was 6.4 months, and the median OS was not reached[8]. The findings demonstrated that the PO approach with NGS profiling was successfully implemented in daily clinical practice for patients with advanced malignancies and led to improved treatment outcomes.

On the other hand, an analysis by Lau *et al*. (2024) evaluated the response and survival of precision-guided treatment (PGT) among 384 high-risk paediatric cancer patients. A total of 256 (67%) patients received PGT recommendations, and 110 (29%) received a recommended treatment. The types of targeted therapy in relation to the drug target are summarised in **Figure 4**. The result indicated that PGT yielded a 3-year OS of 34% in the 384-patient cohort. Remarkably, PGT achieved a 36% objective response rate (ORR) (complete response [CR]: 9% and partial response [PR]: 27%) and stable disease in 34% of patients. Moreover, PGT also improved 2-year progression-free survival (PFS) compared with standard of care (SOC) (26% vs 12%, p=0.049, **Figure 5A**) or targeted agents not guided by molecular findings (UGT) (26% vs 5.2%, p=0.003, **Figure 5B**)[9]. The results confirmed that PGT informed by molecular profiling significantly improves outcomes for children with high-risk cancers.

The survival benefits of the PO approach in patients with end-stage cancers were demonstrated in the prospective study by Mapendano *et al*. (2025). 196 patients with end-stage cancers at a single oncological centre were included, and whole exome and RNA sequencing were performed based on the targeted treatment prescribed. A driver variant was identified in all but 3 patients, whereas 42% were affected simultaneously by more than oncogenic pathways.

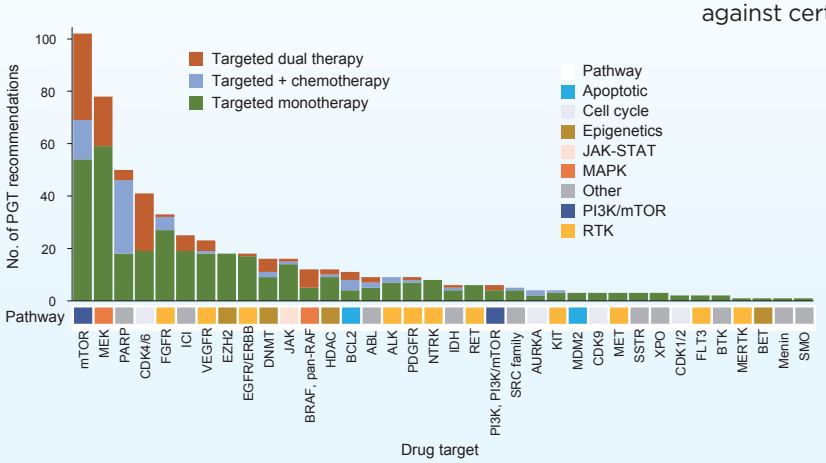

Figure 4. *Types of targeted therapy in relation to the drug target*[9]

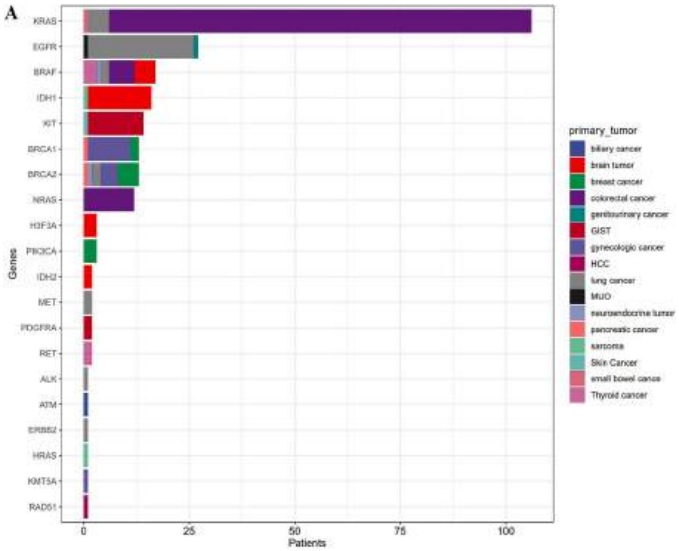

Figure 3. *Genetic alterations identified using NGS profiling in South Korea real-world study*[8]

Notably, druggable targets were suggested in 42% of patients, but two-thirds were not treated. For patients treated (n=30), the clinical benefit rate (CBR) was 44%, and the median time on treatment was 3.5 months. Essentially, the median OS was about 2.6 times longer for patients with a recommended targeted treatment initiated (15.7 months) as compared with patients with no druggable targets (6.5 months, p=0.003) and those who were not treated by targeted drugs (5.8 months, p=0.004, **Figure 6**). The report suggested that targeted treatment was the strongest prognostic predictor[10].

Published clinical data showed that the PO approach yielded significantly better survival benefits compared to the standard treatment; however, PO approach appeared to be feasible in only a small proportion of patients.

Challenges with Precision Oncology Medicines

Undoubtedly, PO approach has revolutionised the landscape of cancer management; however, there are obstacles hindering the clinical applications of PO. For instance, only a small number of patients with specific cancer types may benefit since targeted therapies against certain biomarkers remain unavailable[3]. In 2018, one-third of all human proteins are yet to be studied in detail, and only 3% were targets of at least one approved drug with a known mechanism of action[11]. In this regard, novel approaches to drug development, such as multifunctional drugs, gene silencing, genetic modification, disruption of the target interactome, target degradation, synthetic lethality, or targeted activation of an antitumor immune response, may be effective[3].

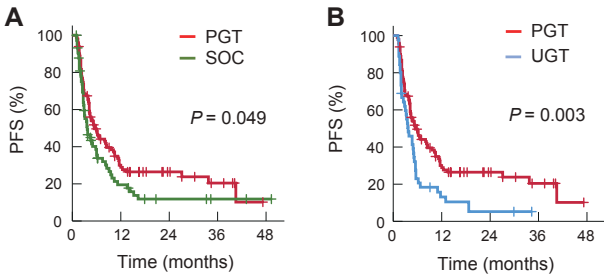

Figure 5. *Types of targeted therapy in relation to the drug target*[9]

Besides, translating the benefits of PO into reality for improving healthcare outcomes is heavily dependent on our ability to identify disease or drug-associated actionable genetic mutations. Accordingly, big data analysis of diverse genomic data and electronic health records provides an efficient and effective way to identify clinically actionable genetic variants for personalised treatments[12].

While NGS provide comprehensive tumour profiles of patients, the cost and throughput advantages of NGS are offset by large trade-offs concerning short sequencing read length and accuracy. Particularly, its high error rate makes it extremely difficult to detect single nucleotide polymorphisms (SNPs) or low-abundance mutations. In this regard, it has been suggested that the dual-base sequencing strategy, where each sequencing run provides only an ambiguous sequence with a partially defined base composition, can provide an inherent proofreading function, thereby reducing errors in the original data[13].

Moreover, interpreting NGS test results remains challenging in practice, making it difficult to administer genomically matched therapies. Remarkably, restrictions on the off-label use of matched drugs may also limit the use of PO-recommended treatments.

The Next Step in Precision Oncology

The PO approach has revolutionised traditional cancer management, and the "one-size-fits-all" cytotoxic treatment is being rapidly replaced by individualised treatment. Emerging clinical investigations demonstrated the improvement in patient outcomes achieved by the PO approach; nonetheless, only a handful number of cancer patients currently benefit from the PO approach due to various technical obstacles. Fortunately, multidisciplinary efforts have been made to optimise PO in clinical settings, particularly with the artificial intelligence (AI), which is anticipated to help overcome these shortfalls.

While PO requires the molecular profiling of tumours to identify targetable alterations, AI allows the integration of vast data derived from multi-omics analyses. Moreover, AI is expected to play a crucial role in future image analysis in radiological oncology. The technology would enhance the accuracy and efficiency from upstream image reconstruction, registration, segmentation, disease diagnosis, and plan optimisation to therapy prognosis and prediction[14].

Apart from diagnostic procedures, AI is expected to facilitate the development of new biomarkers for precise disease characterisation by allowing the processing of vast, heterogeneous datasets to identify variables most strongly correlated with specific clinical outcomes. These variables are then integrated into predictive algorithms for use with new patient data[15].

Although the application of AI to PO is still in the early phase, emerging literature has provided an insight into its future applications in cancer management. The dawn of treatment enhancement with PO is emerging and, more importantly, this improvement will help make a difference to the lives of oncology and non-oncology patients in near future.

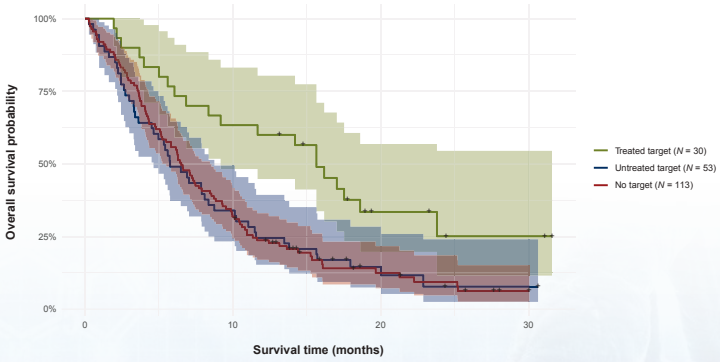

Figure 6. *OS of end-stage cancer patients according to targeted treatment groups*[10]

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1. Schwartzberg et al. *American Society of Clinical Oncology Educational Book* 2017; 160–9. **2.** Ding et al. *Mol Cancer Res* 2018; 16: 269–78. **3.** Rulten et al. *Int J Mol Sci* 2023; 24. DOI:10.3390/IJMS241612613. **4.** Steuten et al. *JCO Clin Cancer Inform* 2019; 3: 1–10. **5.** Pei et al. *Cells 2023, Vol 12, Page* 493 2023; 12: 493. **6.** Qin. *Cancer Biol Med* 2019; 16: 4. **7.** Gremke et al. *Cancers (Basel)* 2024; 16: 1561. **8.** Kim et al. *Scientific Reports* 2025 15:1 2025; 15: 1–14. **9.** Lau et al. *Nature Medicine* 2024 30:7 2024; 30: 1913–22. **10.** Mapendano et al. ESMO Open 2025; 10: 104089. **11.** Oprea et al. *Nat Rev Drug Discov* 2018; 17: 317–32. **12.** Carter et al. *J Healthc Eng* 2016; 2016. DOI:10.1155/2016/3617572. **13.** Cheng et al. *Front Bioeng Biotechnol* 2023; 11: 982111. **14.** Cui et al. *Br J Radiol* 2023; 96: 20230142. **15.** McGale et al. *Oncotarget* 2024; 15: 588.

Self Study Questions (1 CME point):

1. Which of the following is/are "omic" methods for profiling molecular characteristics of tumours?

i. DNA sequence data
ii. Protein levels
iii. Cellular metabolism

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

2. Which of the following regarding next-generation sequencing (NGS) is/are correct?

i. It involves DNA/RNA fragmentation
ii. Targeted DNA is broken down into segments of 40-50bp in length
iii. PCR amplification may be involved

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

3. According to the study regarding routine clinical practice in South Korea by Kim et al. (2025), which of the following is the most frequently altered gene detected in the patients with advanced solid tumours?

A) KRAS
B) EGFR
C) BRAF
D) BRCA

4. Which of the following is/are factors hindering the clinical applications of PO?

A) Limited number of actionable mutations identified.
B) High error rate of NGS in detecting SNPs or low-abundance mutations.
C) Restrictions on the off-label use of matched drugs.
D) All of above.

5. According to the article, which of the following is/are potential benefit(s) of AI in optimising PO?

i. Improving the efficiency of multi-omics analyses
ii. Enhancing the accuracy and efficiency image analyses in radiology
iii. Predicting the onset of relapsed diseases

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

This CME article was prepared by Dr. Mohsin Roshan and Dr. Roy Yuen Chi Lau and accredited by the Hong Kong Doctors Union (HKDU).

Please submit your answers via digital V.Pulse at vpulsehk.com or scan the QR code **before 20-Mar-2025**:

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by Dr. Mohsin Roshan

Haemato-Oncology

A New Treatment Era with Daratumumab in Transplant-eligible Newly Diagnosed MM Patients

Multiple myeloma is a clonal plasma cell proliferative disorder that is often diagnosed in individuals aged 65 to 74 years[1]. Notably, the treatment landscape of MM has evolved over the last few years with availability of newer agents and combination treatments[2]. Daratumumab (DARA), a fully human monoclonal antibody[3] has recently shown promising results as a combined induction and consolidation agent in the CASSIOPEIA study[4]. The long-term outcomes (> 6-Year Update) from CASSIOPEIA were presented at the 2024 European Haematology Association (EHA) on June 14th, 2024, in Madrid, Spain by Professor Philippe Moreau, a world-renowned haematology specialist.

Revolutionising Treatment for Transplant-eligible NDMM Patients

MM is a clonal plasma cell proliferation disorder with abnormally elevated serum monoclonal immunoglobulins, often resulting in severe end-organ damage when left untreated. It is frequently diagnosed among individuals aged 65 to 74 years, with a median age of 69 years[1]. Interestingly, MM accounts for approximately 2% of the cancers diagnosed and 10% of haematologic malignancies in the United States (U.S.). The diagnostic criteria for MM typically include ≥ 10% clonal plasma cells in bone marrow, demonstrable end-organ damage and specific myeloma-defining biomarkers[5]. The treatment landscape of MM has evolved over the last few years with availability of many newer agents and combination treatments that has now been routinely incorporated for newly diagnosed MM patients (NDMM). However, the multitude of treatment options may also present a challenge to select the best options tailored to specific patient situation[2]. DARA, a fully human monoclonal antibody targeting clusters of differentiation 38 (CD38) has received the Food and Drug Administration (FDA) approval in 2019 as treatment for adult with MM in combination with bortezomib, thalidomide and dexamethasone in NDMM patients who are eligible for autologous stem cell transplant (ASCT)[3].

Efficacy of DARA was investigated in CASSIOPEIA, a two-part, open-label, randomised active-controlled phase 3 study comparing induction and consolidation treatment with daratumumab 16 mg/kg in combination with bortezomib, thalidomide, and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with NDMM eligible for ASCT[4]. In part 1 of the study, patients were randomly assigned (1:1) to receive either 4 pre-transplant induction and 2 post-transplant consolidation cycles of VTd alone (VTd group) or in combination with DARA (D-VTd group), with a median follow-up of 18.8 months from first randomisation. The primary endpoint of the first part of the trial (part 1) was stringent complete response assessed 100 days after transplantation. Remarkably, the results demonstrated that addition of DARA to VTd before and after ASCT improved the depth of response and significantly prolonged the PFS, as well as overall survival (OS) with acceptable safety profile in NDMM patients[4]. During the second part of the trial (part 2), 886 patients still on the study post-consolidation (day 100 post-ASCT) who had experienced partial response or better (458 [84%] of the D-VTd group; 428 [79%] of the VTd group) were randomly assigned between May 2016 to June 2018 to receive either daratumumab maintenance (n=442 [229 from D-VTd group, and 213 from the VTd group]) or observation only (n=444 [229 from the D-VTd group, 215 from the VTd group]) with a median follow-up of 35.4 months from second randomisation. The primary endpoint was PFS from second randomisation and astonishingly, DARA maintenance every 8 weeks for 2 years significantly improved the PFS (hazard ratio [HR]: 0.53 [95% confidence interval (CI): 0.42-0.68];

P<0.0001) and achieved higher rates of minimal residual disease (MRD) compared to the observational group[6].

D-VTd have profound effects on survival as induction/consolidation and maintenance monotherapy[7]

Long-Term Survival Benefit with Daratumumab Combined Treatment:

The long-term study outcomes of CASSIOPEIA were evaluated by Moreau et al. (2024) and data from part 1 of the study with 1,085 patients who were randomly assigned to D-VTd (n=543) or VTd (n=542) between 22nd September 2015 and 1st August 2017 were included. Similarly, data from the part 2 of the CASSIOPEIA was included where 886 patients who were re-randomised to DARA maintenance (n=442) or observation (n=444) between 30th May 2016 to 18th June 2018[7]. The median follow-up was 80.1 months (interquartile range [IQR] 75.7-85.6 months) from first randomisation and 70.6 months (66.4-76.1) from second randomisation with a total of 1,053 patients entered the follow-up phase. The median PFS (mPFS) for first randomisation regardless of second randomisation was significantly longer for the D-VTd group (83.7 months [95% CI: 70.2 not estimable (NE)]) than for the VTd group (52.8 months [47.5-58.7]; HR 0.61 [95% CI: 0.52-0.72]; p<0.0001)[7].

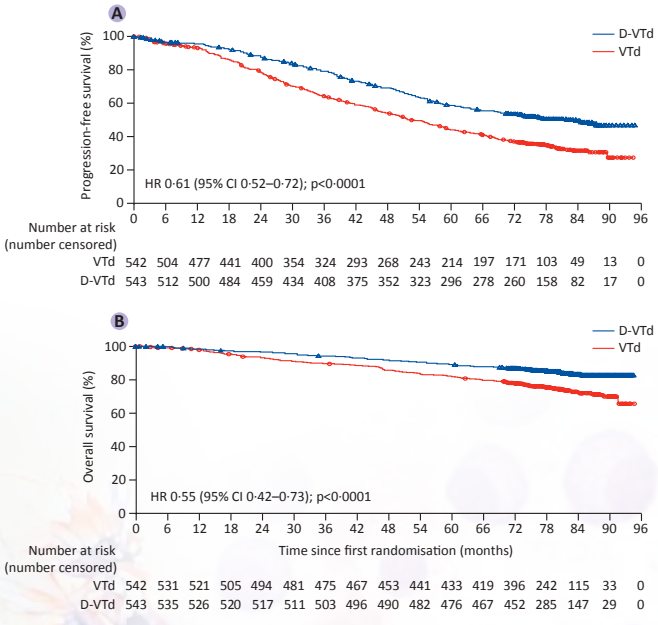


*Figure 1. Progression-free survival and overall survival from first randomisation regardless of second randomisation in the intention-to-treat population (n=1085)[7] with median follow-up of 80.1 months. (**A**) Progression-free survival. (**B**) Overall survival. D-VTd=daratumumab in combination with bortezomib, thalidomide, and dexamethasone. HR=hazard ratio. VTd=bortezomib, thalidomide, and dexamethasone.*

Similarly, the OS from first randomisation regardless of second randomisation was significantly longer in the D-VTd group than the VTd group (estimated 72-month OS rate of 86.7% [95% CI: 83.5-89.3] in D-VTd group vs 77.7% (73.9-81.0) in VTd group, respectively), conferring a 45% risk reduction of death with D-VTd compared to VTd (**Figure 1**)[7].

During the maintenance phase with a median follow-up of 70.6 months from second randomisation, the PFS was significantly longer in the DARA maintenance group compared to the observation group (HR: 0.49 [95% CI: 0.40-0.59]; p<0.0001). However, the mPFS was not reached (95% CI: 79.9-NE) in the DARA group vs 45.8 months (41.8-49.6) in the observation group. The estimated 72-month PFS rates were 57.1 (52.1-61.7) in the DARA group and 36.5% (31.9-41.2) in the observational group; DARA maintenance reduced the risk of progression or death by 51% compared to the observational group[7]. Notably, the PFS was significantly longer in patients who received D-VTd plus DARA maintenance vs D-VTd plus observation (HR: 0.76 [95% CI: 0.58-1.00]; p=0.048). The estimated 72-month PFS was 60.3% in D-VTd plus DARA group compared to only 50.5% in the D-VTd plus observational group (**Figure 2**)[7].

The longest PFS was observed in patients who received D-VTd plus DARA maintenance[7]

Durable MRD-Negativity Achieved with Daratumumab Regimen in NDMM Patients

Achieving MRD-negativity is a strong and independent prognostic factor in both prospective randomised clinical trials and in the real-world setting[8]. The

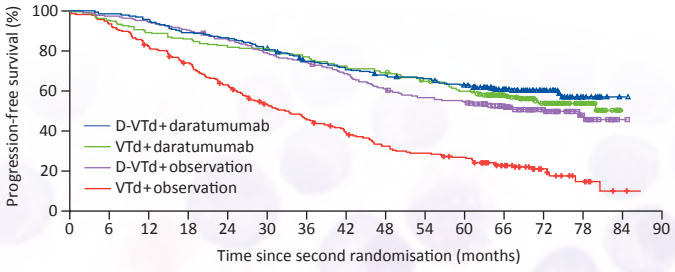


Figure 2. Progression-free survival from second randomisation in the maintenance-specific intention-to-treat population (n=886). Progression-free survival from second randomisation by induction and consolidation and maintenance therapies. Daratumumab and observation were the two randomly assigned (1:1) treatments at second randomisation; therefore, these are the comparisons with HRs, 95% CIs, and p values provided in the further breakdown of the data by induction and consolidation treatment (D-VTd or VTd)[7]. HR=hazard ratio. D-VTd=daratumumab in combination with bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.

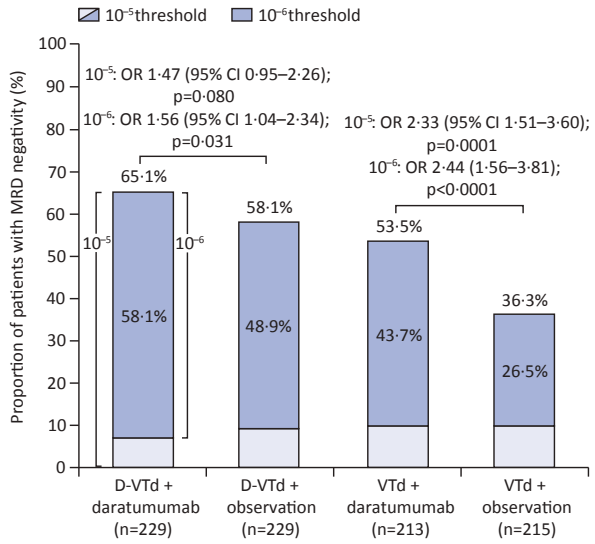


Figure 3. Proportion of patients with a complete response or better and MRD-negativity at any timepoint from post-consolidation onwards in the maintenance-specific intention-to-treat population (n=886). MRD was assessed using bone marrow aspirates via next-generation sequencing[7]. MRD=minimal residual disease. OR=odds ratio. D-VTd=daratumumab in combination with bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.

CASSIOPEIA study utilised multiparametric flow cytometry to measure the MRD-negativity rate and demonstrated a higher rate of MRD-negativity in D-VTd group compared to the VTd group after both the induction and consolidation therapies. During the maintenance phase of the study, the reported MRD-negativity was higher in the D-VTd plus DARA group compared to the D-VTd plus observation group at 10^{-6} sensitivity threshold. Similarly, the proportion of patients reported with MRD-negativity was higher in the VTd plus DARA group than the VTd plus observation group at the 10^{-5} and 10^{-6} thresholds, respectively (**Figure 3**)[7].

The post-hoc analysis showed that the proportion of patients with sustained MRD-negativity for 12 months or longer was higher in the D-VTd plus DARA group than the D-VTd plus observation group at both the 10^{-5} and 10^{-6} sensitivity thresholds, respectively. The proportion of patients with sustained MRD-negativity for 24 months or longer was also higher in the D-VTd plus DARA group than D-VTd plus observation group at both sensitivity threshold (**Figure 4**)[7]. Additionally, the proportions of patients with sustained MRD-negativity for 12 months or longer and for 24 months or longer were also higher in the VTd plus DARA group than in the VTd plus observation group at both sensitivity thresholds[7]. A higher proportion of patients who received subsequent therapy received an anti-CD38-based first subsequent therapy in the observation group (61% in the D-VTd plus observation group and 68% of VTd plus observation group) compared to the DARA maintenance group (38% in D-VTd plus DARA group and 40% in VTd plus DARA group). Among the anti-CD38-based treatment, the most common subsequent therapy regimen was DARA, lenalidomide and dexamethasone (D-Rd)[7]. Interestingly, the PFS on next line of therapy from second randomisation was longer in DARA maintenance group than in the observation group[7], highlighting the importance of early inclusion of DARA in the treatment regimen.

Highest Sustained MRD-negativity rates reported in D-VTd/DARA group for ≥12 and ≥24 Months[7]

Consistent Long-term Safety in NDMM Patients at ~6 Year Follow-up

As the survival times of MM patients continue to improve, second primary malignancies (SPM) have become an increasingly relevant long-term risk among MM survivors[9]. The long-term follow-up of CASSIOPEIA revealed that the risk of SPM observed during the maintenance phase was relatively low and consistent in all arms of the treatment throughout the 6 years follow-up (11% of 229 patients in the D-VTd plus DARA group, 6% of 229 patients in D-VTd plus observation group, 12% of 211 patients in the VTd plus DARA group, and 10% of 215 patients in the VTd plus observation group)[7]. The CASSIOPEIA study represents as one of the longest durations of follow-up in transplant-eligible patients with NDMM to date with median follow-up of nearly 7 years from first randomisation. The study also highlighted that the addition of DARA to VTd induction and consolidation had a significantly lower risk of disease progression or death than patients treated with VTd only.

Furthermore, the median PFS was approximately 2.5 years longer with the addition of DARA to the VTd regimen in NDMM patients. In terms of maintenance, PFS benefit was observed in patients who received D-VTd plus DARA maintenance and VTd plus DARA maintenance compared to those who only received observation (D-VTd plus observation and VTd plus observation)[7]. Therefore, it can be concluded that patients treated with D-VTd plus DARA maintenance show a clinically superior PFS outcomes and DARA maintenance improves PFS, even when accounting for the effects of induction and consolidation therapies. More notably, NDMM patients treated on VTd regimen experienced a longer PFS with next line of therapy with DARA (VTd plus DARA) compared to VTd plus observation. The reported clinical benefits of D-VTd

regimen were complemented by observations reported in the phase 3 PERSEUS and phase 2 GRIFFIN studies[7].

Consistently low incidence of second primary malignancies up to ~6 Year of Follow-up[7]

Conclusion

D-VTd induction and consolidation therapy followed by DARA maintenance therapy leads to a high and durable rates of MRD-negativity, which translates to superior PFS outcomes[7]. These results confirm D-VTd as a viable treatment option for induction and consolidation, followed by subsequent DARA monotherapy maintenance for transplant-eligible NDMM patients.

D-VTd induction/consolidation as a standard of care with demonstrated benefits on addition of DARA monotherapy maintenance in transplant-eligible NDMM patients[7]

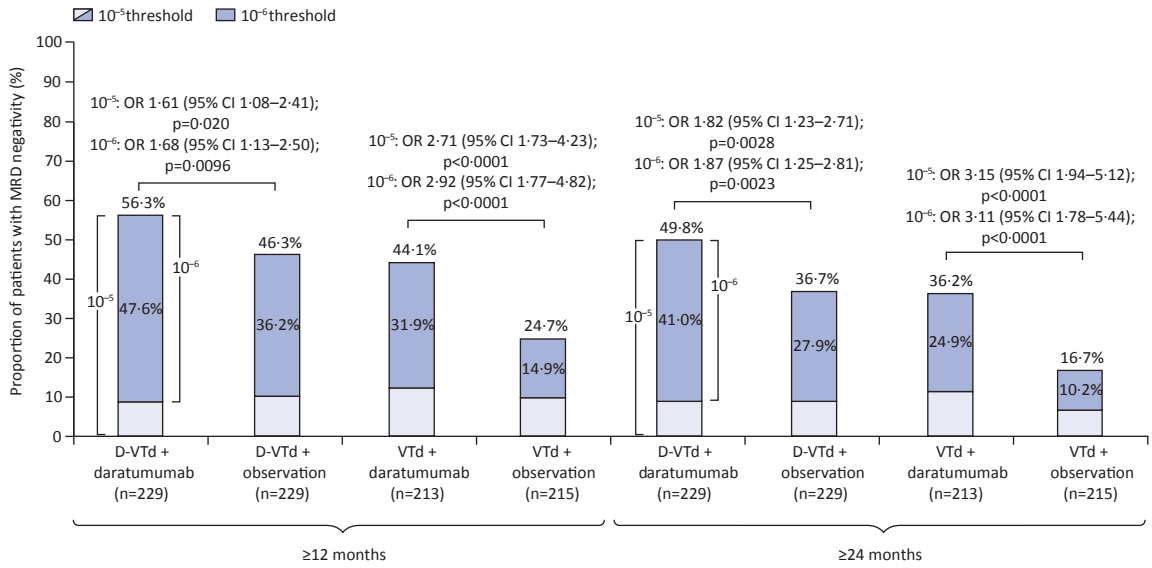
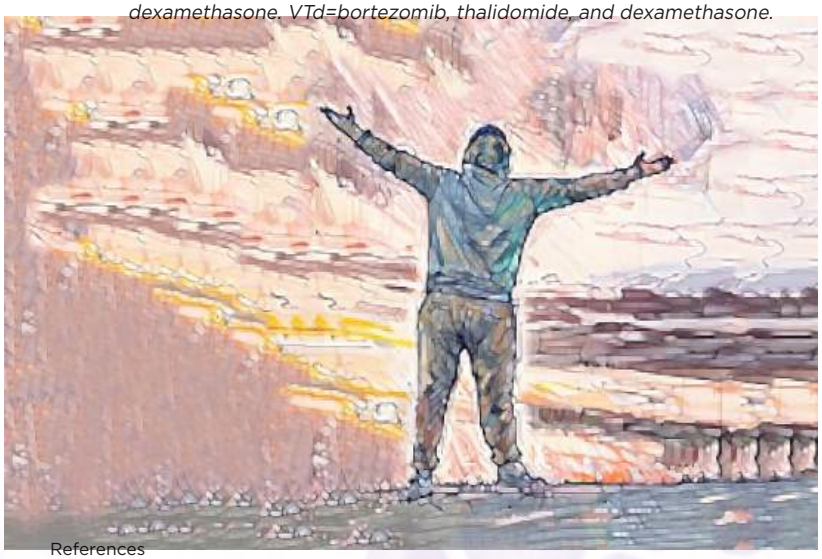


Figure 4. Post-hoc analysis of the proportion of patients with a complete response or better and sustained MRD negativity at any timepoint from post-induction onwards in the maintenance-specific intention-to-treat population (n=886). MRD was assessed using bone marrow aspirates via next-generation sequencing[7]. CI= confidence interval. MRD=minimal residual disease. OR=odds ratio. D-VTd=daratumumab in combination with bortezomib, thalidomide, and dexamethasone. VTd=bortezomib, thalidomide, and dexamethasone.



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by Dr. Roy Lau

Are We Doing Our Best to Reduce the Risk of HCC in HBV Patients?

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. Essentially, persistent hepatitis B virus (HBV) infection is one of the most important risk factors for HCC[1]. Thus, targeted strategies to mitigate HBV infection are crucial to minimise the risk of HCC. Accordingly, preventive strategies for HBV-related HCC can be divided into primary, secondary and tertiary prevention[1]. In the 37th Annual Scientific Meeting of the Hong Kong Association for the Study of Liver Diseases (HKASLD), Prof. Tung-Hung Su highlighted the current challenges in various levels of HBV-related HCC prevention. Particularly, the roles of antiviral therapy in reducing HCC risk in HBV patients were discussed.

Primary Prevention – Reducing HCC Risk for All

The goal of primary prevention of HBV-related HCC is to prevent high-risk individuals among the total population from acute HBV infection[1]. Prof. Su suggested that universal hepatitis B vaccination is the strategy utilised by most countries. Indeed, existing literature advocated hepatitis B vaccination as the most cost-effective measure of primary prevention of HBV-related HCC[1]. In Hong Kong, HBV vaccination and hepatitis B immunoglobulin (HBIg) injection to newborns of carrier mothers have been implemented since 1984, and universal neonatal HBV vaccination has been implemented since 1988[2].

Secondary Prevention – Protecting the Individuals at Risk

The aim of secondary prevention of HBV-related HCC is to achieve long-term and profound viral suppression among hepatitis B carriers, whereas antiviral therapy with the monitoring of compliance, efficacy and resistance, as well as HCC surveillance are the key measures[1]. As per the Global Health Sector Strategy on Viral Hepatitis 2016-2021 of the World Health Organisation (WHO), treating 80% of eligible HBV is one of the goals for chronic HBV control[3].

In the scenario of Hong Kong, the reported prevalence of hepatitis B surface antigen (HBsAg)-positive among adults aged 15 to 84 was 6.2% in 2022. Notably, HBsAg prevalence was lower in young adults than those aged 35 or above[4], probably due to the universal neonatal HBV vaccination program implemented in 1988. To achieve the goal of secondary prevention of HBV-related HCC, Prof. Su emphasised that the key issue is to find individuals with HBV who are eligible for antiviral therapy. He highlighted that 31.8% of local HBsAg+ individuals were reported to have HBV viral load ≥2,000 IU/ml[4], at which antiviral therapy should be considered.

Challenges in HCC Prevention

Prof. Su remarked that low treatment uptake among eligible individuals has been the main obstacle in HCC prevention. Essentially, a community-based study by Liu *et al.* (2019) suggested that over 47.6% of local HBsAg+ individuals did not know their HBV carrier status[5]. Hence, Prof. Su commented that more effort is needed to increase disease awareness of HBV. Moreover, while 31.8% of local HBsAg+ individuals were reported to be eligible for antiviral therapy, only 13.5% had ever received antiviral therapy[4]. Thus, in addition to finding individuals with HBV, promoting antiviral therapy among eligible patients is of paramount importance.

In order to achieve the goal advocated by the WHO by 2030, more individuals with HBV have to be identified and treated. Accordingly, the WHO has addressed new guidelines for managing Chronic HBV (CHB) infection. Particularly, the new guidelines have expanded and simplified treatment criteria for adults and adolescents aged over 12 years, with conditions such as significant cirrhosis and persistently abnormal alanine transaminase (ALT) levels[6]. Given clinical tests for liver fibrosis or cirrhosis, HBV viral load, and ALT levels are readily available in Hong Kong, Prof. Su suggested that we can broaden the scope of eligible individuals receiving antiviral treatment against HBV in accordance with the new WHO guidelines.

Selecting the Appropriate Antiviral Therapy

Apart from broadening the scope of eligible individuals, Prof. Su pointed out that another issue governing the effective prevention of HBV-related HCC is the choice of antiviral therapy with higher potency and lower resistance. In this regard, a local retrospective study including clinical data of 29,350 CHB patients by Yip *et al*. (2020) compared the outcomes of tenofovir disoproxil fumarate (TDF) and entecavir (ETV). After a median follow-up time of 3.6 years, TDF was associated with a significantly lower risk of HCC than ETV (**Figure 1**) after propensity score (PS) weighting (weighted sub-distribution hazard ratio [SHR]: 0.36, p=0.013) and after adjusting for HBV DNA suppression and ALT normalisation at 1 year (n=17,712, SHR: 0.35, p=0.047)[7].

Interestingly, Prof. Su reviewed a series of published meta-analyses comparing the efficacy of TDF in reducing HCC risk against ETV. He summarised that the hazard ratios (HR) reported in the majority of published meta-analyses were broadly similar, and most of the results favoured TDF.

On the other hand, a national-wide study by Kim *et al*. (2023) reported that, among 11,537 PS-matched treatment-naïve CHB patients who received tenofovir alafenamide (TAF) or TDF between 2017 and 2022

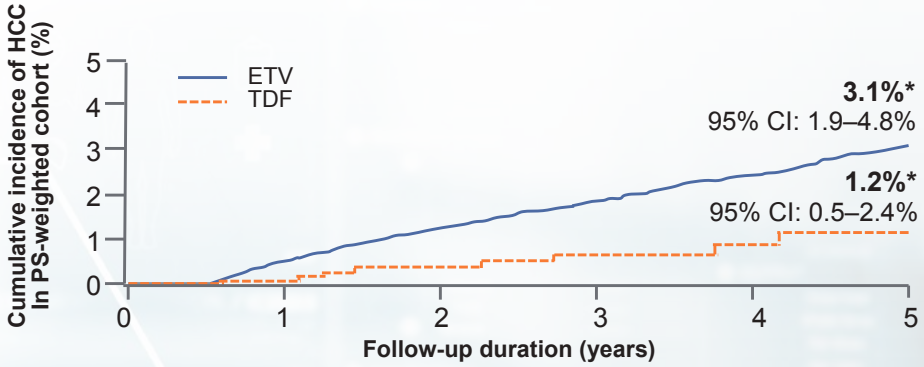

Figure 1: Cumulative incidence of HCC in CHB patients treated with TDF and ETV[7]

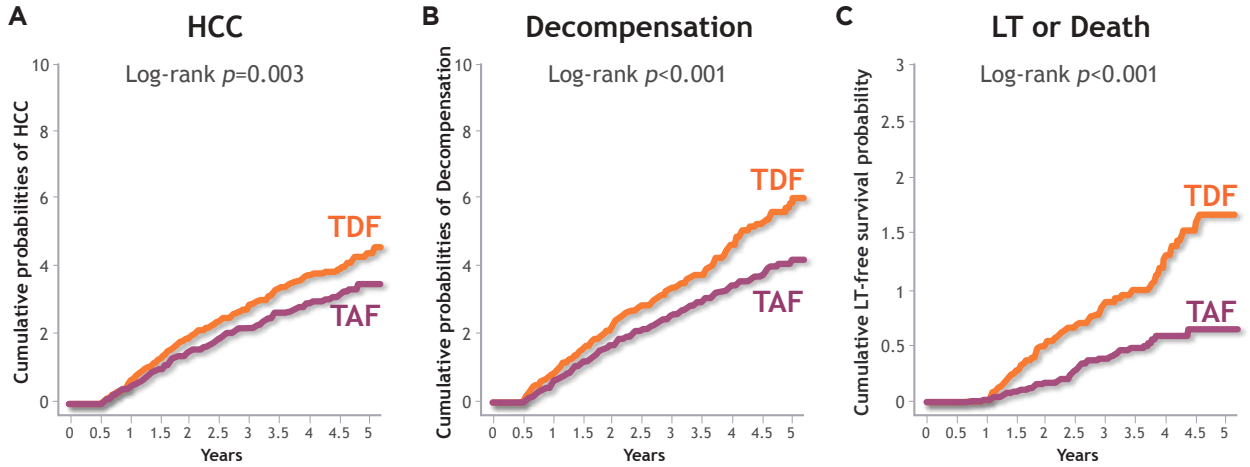

Figure 2: *Cumulative incidence of liver-related clinical outcomes in CHB patients treated with TAF or TDF, A) HCC, B) LT or death, C) decompensation*[8]

in Korea, TAF was associated with significantly lower risks of HCC (HR: 0.77, p=0.003, **Figure 2A**), liver transplantation (LT) or death (HR: 0.43, p<0.001, **Figure 2B**), and decompensation (HR: 0.74, p<0.001, **Figure 2C**) compared to TDF. Notably, the results were valid regardless of liver cirrhosis status[8]. Hence, the results showed that TAF is associated with better liver-related clinical outcomes versus TDF among CHB patients.

Remarkably, the long-term impact of low-level viremia (LLV, <2,000 IU/ml) among individuals with HBV has been demonstrated in the retrospective study by Kim *et al*. (2017), which involved 875 treatment-naïve HBV-infected patients. The study suggested that, during a median 4.5 years of follow-up, HCC developed more frequently in patients who experienced LLV than those who maintained virological response (MVR, 14.3% vs 7.5% at 5 years, p=0.015). Furthermore, among patients with cirrhosis, those with LLV exhibited a significantly higher HCC risk than those with MVR at 5 years (adjusted HR: 2.20, p=0.002)[9].

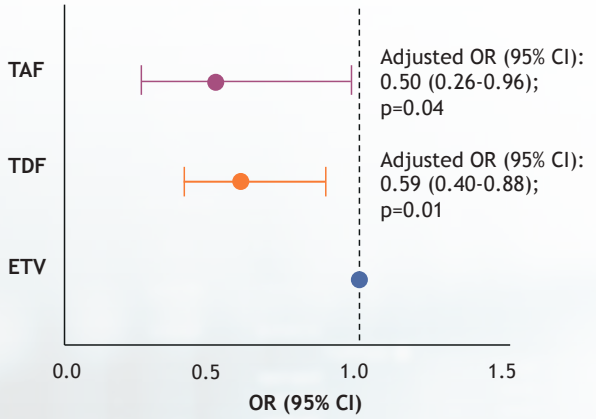

Figure 3: *Adjusted OR for LLV risk*[10]*, CI: confidence interval*

While LLV is shown to be associated with unfavourable outcomes in individuals with HBV, an analysis of 1,043 CHB patients by Wang *et al*. (2022) indicated that TDF (n=284) and TAF (n=74) could significantly reduce the risk of LLV in CHB patients in the binary logistic regression analysis compared with ETV (n=685; [TDF vs ETV] adjust odds ratio [OR]: 0.59, p=0.01; [TAF vs ETV] adjust OR: 0.50, p=0.04, **Figure 3**)[10].

Of importance, a real-world prospective study of 247 ETV-treated patients by Ji *et al*. (2021) suggested that switching ETV-treated patients with LLV to TAF resulted in significantly better complete virologic response and ALT normalisation compared with patients who continued ETV therapy (**Figure 4A and 4B**)[11]. For patients with LLV, Prof. Su suggested we check the patient's compliance with the prescribed treatment and consider switching to another class of therapy to improve viral suppression.

Tertiary Prevention – Minimising the Risk of HCC Recurrence

The essence of tertiary prevention is to improve liver reserve and reduce HCC recurrence after curative therapy by prescribing antiviral therapy[1]. Prof. Su shared the findings of a recent study by Chang *et al*. (2024) involving 390 HBV-related HCC patients with curative treatment for HCC and treated with ETV (n=328) or TDF (n=62) between January 2011 and December 2020. Compared to the ETV group, TDF users had lower all-cause mortality (adjusted HR:0.38, p=0.003) and HCC-related mortality (adjusted HR: 0.23, p=0.005). Most importantly, there are significantly greater patients with fibrosis-4 (FIB-4) score ≤1.45 in the TDF group compared with ETV group, either at 6 months (81% vs 61%, p=0.044), 12 months (86% vs. 59%, p=0.002), and 24 months (82% vs. 49%, p=0.002), respectively. The percentage of patients with albumin-bilirubin (ALBI) grade 3 were also significantly reduced in the TDF

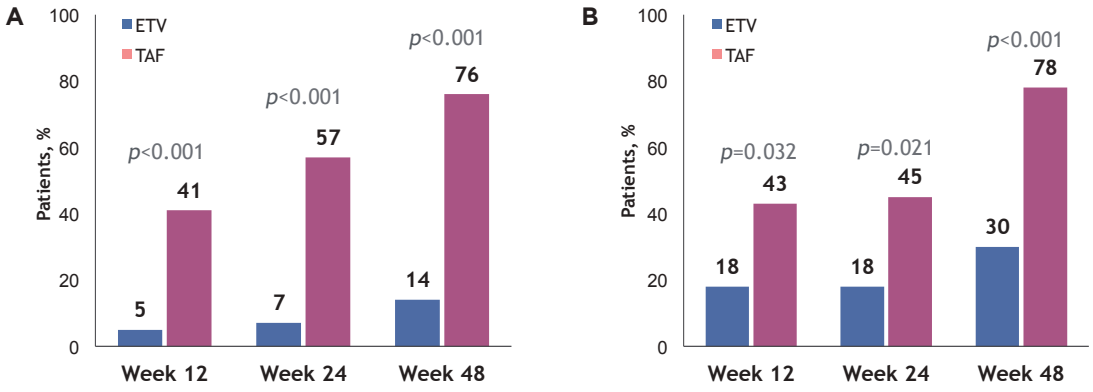

Figure 4: *Improved A) complete virologic response and B) ALT normalisation in ETV-treated patients with LLV upon switching to TAF*[11]

group, at 12 months (28% vs. 46%, p=0.013), and 24 months (10% vs. 50%, p<0.001), compared with ETV (**Figure 5**)[12]. Hence, the results favoured TDF therapy in reducing the risk of HCC-related outcomes among patients with HBV-related HCC after curative treatment compared with ETV.

Doing Best to Reduce the Risk of HBV-related HCC

In reducing the risk of HCC in HBV individuals, Prof. Su emphasised the importance of universal screening in finding more eligible patients and timely prescribing antiviral therapy. Particularly, maintaining good viral suppression and ALT normalisation are crucial for controlling the risk of HBV-related HCC. Therefore, it is important to select a potent antiviral therapy for individuals with HBV and HCC patients after curative treatment. Based on existing clinical data, tenofovir-based therapy (TDF or TAF) would be a preferred therapy to provide better outcomes for HBV patients in certain scenarios.

Figure 5: *Trend of FIB-4 score and ALBI grade in curatively treated HBV-related HCC under ETV or TDF treatment*[12]

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Neurology

Improving Somnolence with Once-daily Perampanel Tablet in Epileptic Patients: A Case Report

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Case Presentation

A 35-year-old male, diagnosed with generalised tonic-clonic seizures (GTCS) in May 2023 following his hospitalization in China for his first seizure attack, consulted Dr. Fung's clinic due to complaints of somnolence that has been affecting his work as a chef.

The patient was found to have abnormal electroencephalogram (EEG) since age 6 and had regular neurology follow-ups until age 15 without any clinical symptoms until the recent hospitalization. Notably, the patient had a strong family history of epilepsy, including his father, uncle, and cousins.

During his recent hospitalization, EEG displayed occasional generalized epileptiform discharge, while the CT brain results were unremarkable except for cortical calcification in the right parietal lobe, ruling out structural pathology. Hence, he was prescribed sodium valproate 500 mg twice daily (BD) but decided to self-reduce the dose to 250 mg in the morning and 500 mg in the evening. He reported no further seizures during the clinic visit.

Clinical examination and investigations

Upon examination, the patient had a blood pressure of 134/88 mmHg and a pulse of 75 beats per minute (bpm). In addition, no focal neurological signs (Romberg test negative) were observed, and the patient had a normal gait. The blood workup was unremarkable.

Treatment and outcome

During the patient's initial visit to Dr. Fung's clinic in early September 2023, he was prescribed perampanel 2 mg once daily (QD) at bedtime as an add-on therapy. Remarkably, after adding perampanel 2 mg, he remained free of seizures, and the dose of his perampanel was titrated to 4 mg bedtime. Meanwhile, the dose of sodium valproate was de-escalated to 250 mg BD. Subsequently, during the 3-week follow-up, the patient remained seizure-free and had no more somnolence, allowing him to carry on with his work.

Dr. Fung herein elaborated that the seizures were effectively controlled with only perampanel 4 mg/day monotherapy since the patient had already discontinued sodium valproate in early October 2023. Indeed, perampanel has been shown to improve sleep architecture in epileptic patients without worsening daytime sleepiness[1] and this case is a notable example of such positive effects, according to Dr. Fung.

Conclusion

Once-daily perampanel at bedtime is an effective and well-tolerated adjunctive therapy for GTCS patients without causing daytime sleepiness.

Perampanel has been shown to improve sleep architecture in epileptic patients...

Perampanel can Effectively Control Seizures without Impacting the Sleep-Wake Cycle in Patients with Epilepsy

Introduction

Among patients with epilepsy, sleep disturbances can worsen the seizure control[1]. A prospective open label study evaluated the effect of the antiepileptic drug perampanel on sleep architecture in patients with refractory epilepsy. Of 25 adult patients aged between 18 to 65 years, 17 completed the study. They received add-on perampanel, starting at 2 mg/day at bedtime, increased by 2 mg after 2 weeks and then monthly until the target dose of 4-8 mg/day was reached. The median dose of perampanel used was 6 mg. Polysomnographic (PSG) recording was scheduled 1 week before starting perampanel and the control PSG after 12 weeks under perampanel treatment and at least 4 weeks on stable perampanel dose. In addition, patients completed the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) questionnaires. The primary endpoints were change from baseline in the ESS and PSQI scores, and PSG variables[1].

Results

Among the 17 patients who completed the study, perampanel caused a modest decrease from baseline in mean ESS score (n=13; p=0.126) and PSQI score (n=12; p=0.127). However, the treatment significantly improved sleep parameters (n=17 patients) including total sleep time (p=0.037), sleep latency (p=0.022), sleep efficiency (p=0.015), sleep maintenance index (p=0.005), wake time after sleep onset (p=0.015), and duration of deep sleep (N3) stage (p=0.026). Notably, the increase in the duration of N3 was achieved concomitantly with a significant reduction in awake time (**Figure 1**)[1]. More importantly, 77.8% patients achieved sleep efficiency >85% (p=0.016 vs baseline).

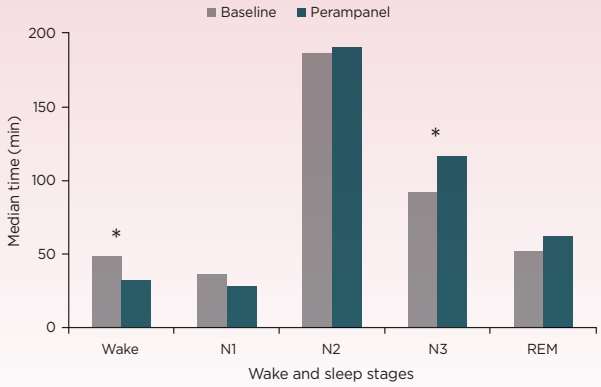

Figure 1: *Median duration of wake and sleep stages (N1, N2, N3 and REM) before and after 12 weeks of perampanel and 4 weeks with a stable dose (4-8 mg q.d.). *p<0.05*[1].

Conclusion

The study concluded that perampanel improved sleep architecture in patients with focal refractory epilepsy without worsening daytime sleepiness[1]. Similar findings were also reported by Fernandes *et al*., (2022) who suggested that perampanel not only reduced sleep-wake cycle disturbance in patients with epilepsy (PWE) but also improved daytime sleepiness[2].

Perampanel improves daytime sleepiness and reduces sleep-wake cycle disturbance in epileptic patients...

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HK-FC-11-001 (Sept 2024)

by Migee Tang

Clinical Trial Snapshot

Conventionally prescribed antipsychotics for schizophrenia primarily target dopamine D2 receptors, leading to a series of side effects like extrapyramidal motor and parkinsonian symptoms[1]. With 20% – 30% patients also experiencing treatment resistance for positive schizophrenic symptoms, there is a pressing need for more effective and safer alternatives[2]. Xanomeline-trospium chloride, the first and only M1/M4 muscarinic agonist, might just fit nicely into this picture[3].

EMERGENT-3[2]

A phase 3, multicenter, double-blind, randomized controlled trial investigating the efficacy and safety of xanomeline-trospium, a new schizophrenia treatment

Objective

To assess the efficacy, safety, and tolerability of xanomeline-trospium in schizophrenia patients experiencing psychosis

Study Population

256 participants

18 – 65 years old

Schizophrenia diagnosis by

- DSM-V
- Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders v.7.0.2

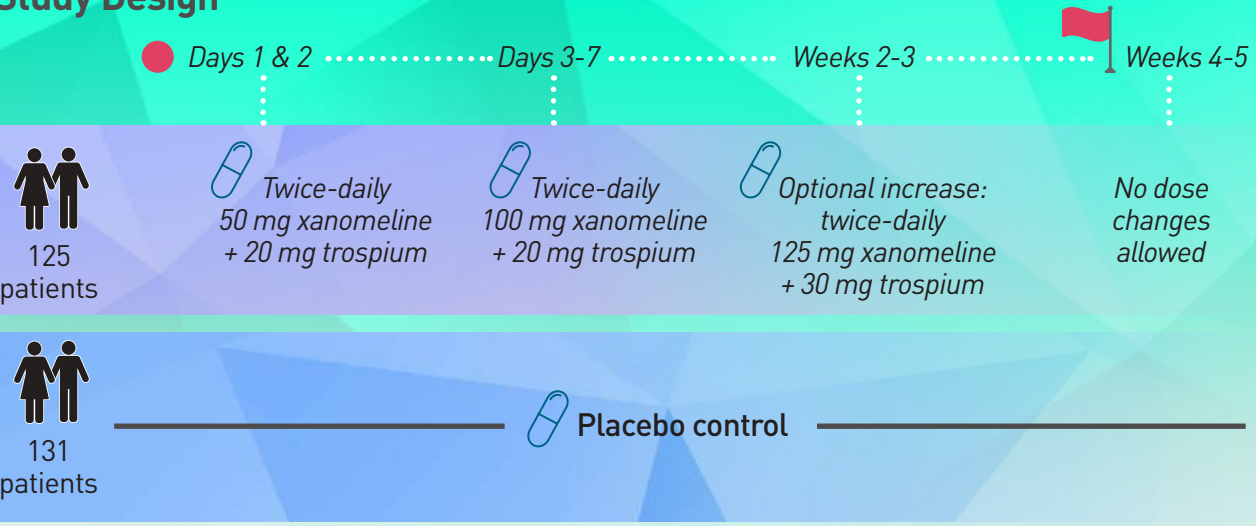
PANSS 80-120

CGI-S ≥4

No primary disorder other than schizophrenia in the last 12 months

No history of antipsychotic treatment resistance

Study Design



Xanomeline-Trospium Chloride – A New Dawn for Schizophrenia Patients

Primary Endpoint

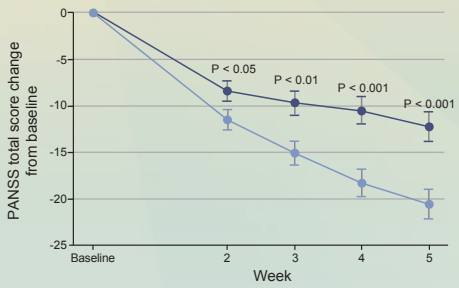
- Change in PANSS total score from baseline to week 5

Secondary Endpoints

- PANSS positive/negative scale score
- PANSS Marder negative factor score
- CGI-score
- Proportion of participants with at least 30% reduction in PANSS score
- Safety

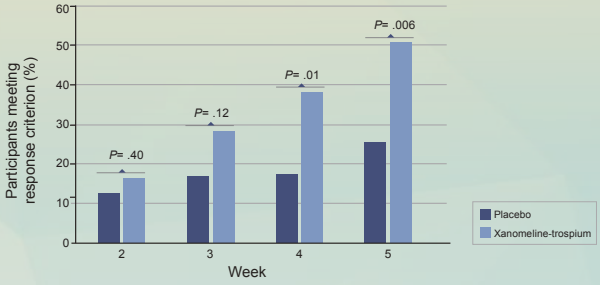
Results

PANSS Total Score



- **8.4 point** greater reduction in xanomeline-trospium group than placebo (P<0.001)

% of Patients with At Least 30% Reduction in PANSS Total Score



- **25.4%** more patients in xanomeline-trospium group than placebo showed ≥30% PANSS score reduction (P<0.01)

Between-group differences in secondary endpoints

PANSS positive subscale score	PANSS negative subscale score	PANSS Marder negative factor score	CGI-S score
3.5 (P<0.001)	0.8 (P>0.05)	0.8 (P>0.05)	0.5 (P<0.001)

- Most common AEs were nausea and dyspepsia
- Rates of SAEs and AEs leading to treatment discontinuation were both similar between the xanomeline-trospium group and placebo group (0.8% vs. 0%; 6.4% vs. 5.5%)

Future Directions

- Head-to-head comparisons of xanomeline-trospium against existing antipsychotic medications
- Twice-daily dosing schedule might lead to problems with adherence
- Long-term efficacy and safety beyond 52 weeks

AE, adverse event; CGI-S, Clinical Global Impression Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; PANSS, Positive and Negative Syndrome Scale

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by Michelle Lee

Personalized NMN: The Catalyst for Functional Improvement

Driven by the strong demand for anti-aging health products, nicotinamide mononucleotide (NMN) has surged in popularity as a health supplement in Hong Kong. NMN is a precursor of nicotinamide adenine dinucleotide (NAD), an enzyme cofactor involved in a variety of biological processes, including aging[1,2]. Aging is identified by downregulation of energy production in mitochondria due to NAD depletion[2]. Restored level of NAD in the body can reverse the mitochondrial decay in aging[2].

Previously, NMN supplement had demonstrated its ability of improving blood NAD level in middle-aged and older individuals[1,3]. However, the relationship between change in blood NAD concentration (NAD_{Δ}) and aging-related functional outcomes has not been investigated[1]. Therefore, Kuerec et al. (2024) evaluted the impact of different doses of NMN supplementation on restoring blood NAD level and its optimal dose for improving health outcomes in middle-aged individuals.

Objective[1]

To investigate the efficacy of different doses of NMN supplementation on blood NAD concentration and their association with age-related functional health outcomes in middle-aged individuals.

Study Design[1,3]

A post-hoc analysis of a randomized, multicenter, double-blind, placebo-controlled, parallel-group, dose-dependent clinical trial conducted in Pune, India.

Key Inclusion:

• Generally healthy individual • Aged 40-65 years • Body mass index (BMI) 18.5-35 kg/m^2

NMN 300 mg (n=20) VS. NMN 600 mg (n=20) VS. NMN 900 mg (n=20) VS. Placebo (n=20)

Key measurements were taken at Baseline, Day 30 and Day 60:

- **BMI**
- **Blood biological age** — Calculated by the Aging.AI 3.0 from blood biomarkers
- **SF-36 score** — A validated 36-item short-form survey (36-SF) for health-related quality of life (QoL) assessment
- **Blood NAD concentration**
- **HOMA-IR** — Homeostatic model assessment for insulin resistance (HOMA-IR) for assessing insulin sensitivity
- **6-minute walk test** — A reliable assessment of the progression of functional exercise capacity in healthy older individuals

The **median effective dose (ED_{50})** of NAD_{Δ} after a 60-day NMN intake was calculated to determine a **target NAD concentration improvement** needed to achieve targeted **significant clinical improvement*** in 50% of the population.

Key Findings[1]

01

Dose-dependently
(p<0.001)
at both Day 30 and Day 60. However, no significant differences were found between the 600 mg and 900 mg NMN groups. (Fig.1)

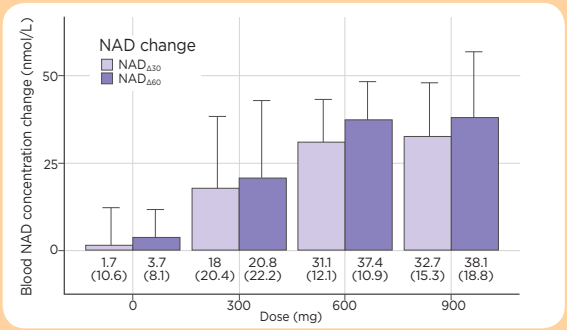


Fig. 1. *Blood NAD concentration change in each dose group. Data are shown in mean (SD). NAD, nicotinamide adenine dinucleotide; SD, standard deviation; Δ30, change at Day 30; Δ60, change at Day 60*

02

75-100% compliance rate with high inter-individual variability in blood NAD concentrations after receiving NMN supplementation

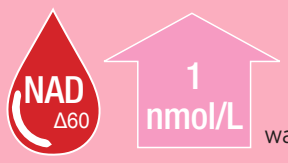
Coefficient of variance (CV) ranging from:
29.2% - 113.3%

03

Higher NAD$_\Delta$ were significantly associated with improvements in functional outcomes

was associated with:

- ↑ **1.37 m** in 6-minute walk test
- ↑ **0.02** in square root of SF-36 scores



was associated with:

- ↑ **2.42 m** in 6-minute walk test
- ↑ **0.02** in square root of SF-36 scores

ED$_{50}$ of NAD$_\Delta$ ≈ 15 nmol/L produced a clinically significant improvement in these outcomes†

04

- No significant association between blood baseline NAD concentration or NAD$_\Delta$ and chronological age or blood biological age, sex, and BMI.

  Individual responses to NMN supplementation may vary widely regardless of these demographic factors.
- A higher baseline HOMA-IR ratio was associated with higher baseline NAD concentration but not with NAD$_\Delta$.
- No significant association between blood baseline NAD concentration and changes in 6-minute walk, SF-36 score, blood biological age and HOMA-IR.

Conclusion[1]

Elevated blood NAD concentration was highly variable between individuals following NMD supplementation

Higher NAD increase was associated with improved functional outcomes and overall QoL.

Despite no established therapeutic window for blood NAD concentration, it should be monitored closely during NMN supplementation. A personalized NMN dosage is crucial in achieving its optimal effects on functional outcomes and

* Significant clinical improvement for the 6-minute walk test was defined as an increase of at least 30 m from the baseline outcome and for the SF-36 score as an increase of at least ten points from the baseline score[1].
† The ED$_{50}$ of NAD$_\Delta$ at Day 60 for the clinically significant improvement of the 6-minute walk test and SF-36 score was 15.65 nmol/L (95% CI: 10.87-20.45 nmol/L) and 13.51 nmol/L (95% CI: 10.54-16.50 nmol/L) respectively[1].

Abbreviations: BMI, body mass index; CI, confidence interval; CV, coefficient of variance; ED$_{50}$, median effective dose; HOMA-IR, homeostatic model assessment for insulin resistance; NAD, nicotinamide adenine dinucleotide; NAD$_\Delta$, change in blood NAD concentration; NMN, nicotinamide mononucleotide; QoL, quality of life; SF-36, 36-item short form survey

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by Dr. Mohsin Roshan

Paediatrics

Flu: An Adversary That Should Not Be Taken Lightly!

Seasonal influenza causes up to a billion infections, globally and approximately half a million deaths. Notably, 10% of seasonal influenza infection occurs in children under the age of 5 and due to poor uptake of the influenza vaccine, there has been a surge of influenza cases during the peak seasons. This article aims to discuss on issues related to poor uptake of influenza vaccine in children and ways to improve the disseminated information on influenza.

Each year, seasonal influenza causes up to a billion infections worldwide, up to 5 million severe cases, and approximately half a million deaths. Notably, approximately 10% of seasonal influenza infections occurs in children under the age of 5 with around 870,000 annual hospitalisations. Furthermore, children under the age of 2 are at high risk of influenza infection due to immature immune system. Interestingly, the prolonged viral shedding in children increases the risk of transmission to vulnerable family member, thus imposing significant cost to individuals and society[1]. Locally, the seasonal influenza is more common in periods from January to March/April and from July to August[2]. The admission rate increases greatly during the peak seasons and reaches up to high-intensity level of more than 8 per 10,000 population among children aged 0-5 years old in Hong Kong[3]. The pathogenic effects of influenza virus are promoted by its continuous evolution through the antigenic drift of its surface proteins haemagglutinin (HA) and neuraminidase. Remarkably, antigenic drift occurs on average 2-8 years in response to the host immune selection pressure and is most frequently seen in influenza A (H3N2), followed by influenza B and influenza A (H1N1)[4].

Influenza virus typically spread via three modes of transmission, namely via droplet, contact and aerosol[5]. In relation to high health risk, annual immunisation with influenza vaccine is recommended for children ≥ 6 months of age, particularly in those with underlying medical conditions[6]. However, despite influenza vaccination is free and subsidised for individuals aged ≥65 years and children aged 6 months to under 6 years in Hong Kong, the uptake remains low (at only at 21%)[3]. The factors contributing to poor uptake of influenza vaccination were mainly related to the safety, and effectiveness of the vaccine. Nevertheless, seasonal influenza is an important health care issue in crowded cities such as Hong Kong where the already strained healthcare system continuously encounters a surge of influenza cases during the peak seasons[3]. The low influenza vaccination uptake among local population was explored further by Sun *et al*. (2018) in a study conducted in 8 focused groups, followed by telephone survey between March and April 2018 with 2,452 respondents (response rate of 41.4%). The study revealed that there was a high uptake of vaccine among children and older adults, suggestive of positive impact of subsidy and outreach programs. However, both the young and middle-aged adults tend to believe their own immunity was sufficient to fend of influenza, thus chose not to vaccinate against the disease[3].

Poor uptake of influenza vaccine puts further strain on the local healthcare system...

To Be or Not to Be Vaccinated?

Since children are particularly at risk for influenza-related complications, vaccination is often recommended; however, in most countries, vaccination coverage is not well reported and remains well below the World Health Organisation (WHO) target of 75%[7]. Many countries recommend the use of live attenuated influenza vaccine (LAIV) for children aged 2 years or older. The trivalent LAIV (LAIV-3) was licensed in the United States (U.S.) in 2003 and had received approval for use in the Europe since 2011[8]. The quadrivalent formulation of LAIV (LAIV-4) subsequently replaced the LAIV-3, however, LAIV-4 was shown to be less effective in children infected with H1N1 strain of influenza A compared to inactivated influenza vaccine, according to a pooled analysis by Chung *et al*. (2019)[9]. The effectiveness of influenza vaccine against influenza-associated hospitalisation in children in Hong Kong during an influenza A (H3N2) epidemic in June to November 2023 was evaluated in a study by Murphy *et al*. (2024). The study included 3,183 children hospitalised with acute respiratory illness in Hong Kong

with influenza A and B viruses detected in 528 (16.6%) children, among which 419 (79.4%) were influenza A (H3N2). The overall vaccine effectiveness against hospitalisation associated with any influenza virus infection was estimated 22.4% (95% confidence interval [CI]: -11.7%, 46.1%) and against influenza A (H3N2) specifically was 14.3 (95% CI: -29.2%, 43.2%)[10].

Recently, a systematic review reported that vaccinated children are 43%-69% less likely to attend hospital for influenza compared to unvaccinated children[11]. The Advisory Committee of Immunisation Practices recommends that children aged <9 years receive 2 doses of influenza vaccine if they have never been vaccinated, with 1 dose considered sufficient in subsequent years. The rationale behind this was that 2 doses in the first year was mainly due to the fact that children of this age group may not yet have exposure to the natural influenza virus infections, there, may lack pre-existing antibodies against some or all influenza virus types/subtypes. Hence, for previously unvaccinated children, the first dose of influenza vaccine is to prime or stimulate the immune response, followed by a second dose to achieve a protective antibody response[12]. The differences between fully vaccinated (vaccinated with 2 doses or, if previously vaccinated those vaccinated with 1 dose) against influenza versus that of partial vaccination (recipient of 1 dose only) in preventing influenza-associated hospitalisation among children in Hong Kong has been evaluated by Chua *et al*. (2019)[12]. Data from 23,187 children aged <9 years admitted to the hospitals with acute respiratory illness from September 2011 through March 2019 demonstrated that the overall vaccine effectiveness (VE) was higher among fully vaccinated children compared to partially vaccinated children (73% vs 31%, respectively) (**Figure 1**)[12]. The influenza vaccination use was recently recommended by the American Academy of Pediatrics (AAP) 2024-2025 policy statement in view of the risk for hospitalisation and death from influenza among children[13].

Influenza vaccine is recommended by the American Academy of Pediatrics (AAP)

Parent Perceptions on Influenza and Vaccination

Considering parents are often the main healthcare decision makers for their young children, understanding parent perceptions towards influenza vaccination remains important for encourage uptake[14]. Interestingly, individuals from different countries have different perception towards the influenza vaccine as a survey carried out in England found that vaccine uptake was associated with parental perception that the influenza vaccine was effective, and their child was susceptible to influenza. Contrarily, the National Flu Survey in the United States (U.S.) suggested that parents' perception that their child was not at risk for influenza or severe illness from influenza or severe illness from influenza was the most common reason for not vaccinating their children. Nevertheless, most of these studies on parental perceptions regarding child influenza vaccination are conducted in Western settings and may not be applicable to Asian setting[14]. The parental perception of Asian parents was explored in a study by Low *et al*. (2017) involving 332 parents of children aged 6 months to 5 years attending pre-schools in Singapore. The results showed that even though the parental knowledge on influenza, benefits of vaccination and willingness to vaccine was high, only 32% of children had ever received influenza vaccine. Furthermore, the study found that parents were more likely to vaccinate their children if it was recommended by the child's doctor and if they felt well informed; thus, this study

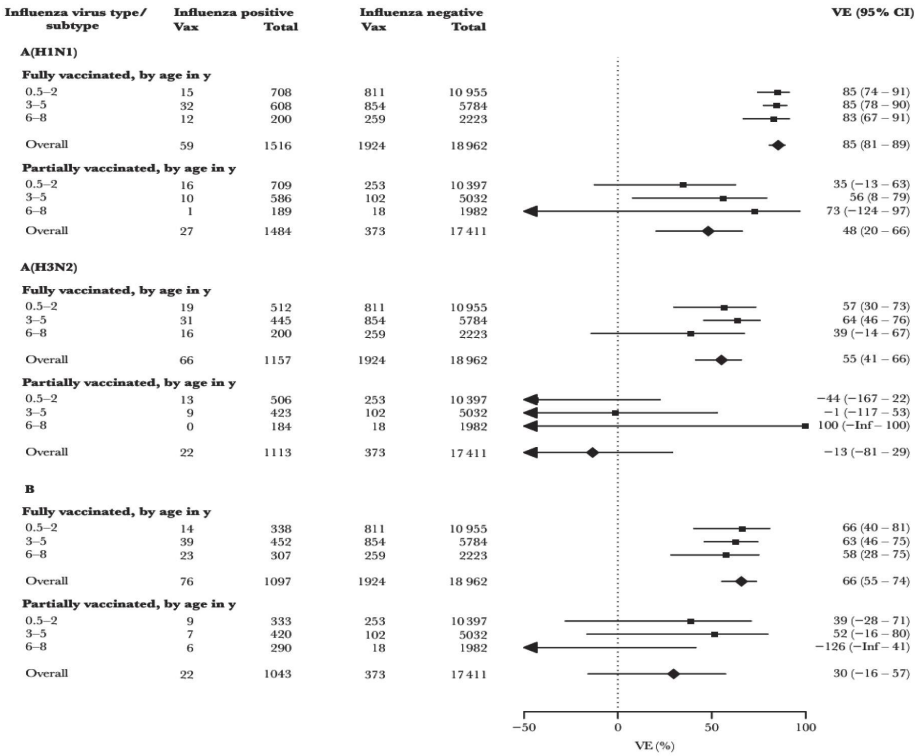

Figure 1: *Vaccine effectiveness (VE) estimates for full and partial vaccination against influenza A (H1N1), A (H3N2), and B viruses separately, by age group[12]. CI, confidence interval.*

revealed that the healthcare professional play a pivotal role in influenza vaccination uptake[14].

Similarly, other studies conducted in China revealed that the parental hesitancy towards seasonal influenza vaccine (SIV) for their children ranged from 34.1% to 43.2%. A study by Cao *et al*. (2024) evaluated reasons for parental hesitancy towards SIV for children in post-pandemic era through online survey of full-time adult factory workers in Shenzhen, China in December 2023. The analysis was based on 1,175 parents who have at least one child under the age of 18 years. Remarkably, the study reported that 37.1% of parents were hesitant to have their index child receive SIV with mothers exhibited lower parental hesitancy toward SIV compared to fathers (31.9% vs 41.3%; p<0.001). The study added that parents who receive more information on SIV were less reluctant to have their children vaccinated compared to those who received less information regarding SIV[15]. Some of the parental misconception to SIV include the concern of vaccine causing the actual flu and the believe that influenza is just a flu and will not harm their children regardless of vaccination[16]. The detrimental effects of influenza cannot be taken lightly as paediatric fatality due to influenza infection was recently reported in Hong Kong where an 8-year-old female developed fever and cough in April 2024 and deteriorated rapidly after her admission. She eventually passed away a day later and was noted to have no previous influenza vaccination[17]. This highlights the need for educational health campaigns to raise awareness and remove misconceptions regarding myths related to the influenza vaccines.

Healthcare providers play a pivotal role in influenza vaccine uptake...

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by Dr. Mohsin Roshan

Internal Medicine (Endocrinology)

A Daily Dark Chocolate, Keeps Diabetes Away!

The global pandemic of type 2 diabetes (T2D) has increased noticeably over the last few dedicates with an estimated 463 million people affected globally since the 2019, which is projected to increased to 700 million by the year 2045[1]. Notably, T2D is a multifactorial disease that is characterised by insulin resistance and impaired insulin secretion, which can lead to severe complications such as microvascular, macrovascular, diabetic nephropathy and retinopathy. Recent public health data has highlighted the importance of prevention, namely through lifestyle factors such as adopting a healthy diet early on. Flavonoids, which are plant-derived phytochemicals has recently gained significant attention since small scale studies has shown an inverse correlation between flavanol intake and incidence of diabetes. Therefore, this literature aims to explain the relationship behind flavonoid intake and lower risk of T2D.

Diabetes in a Glance

Diabetes mellitus (DM) is a global pandemic that affects 1 in 10 individuals aged 20-79 years and ranked among the leading causes of premature mortality. Interestingly, the global incidence and prevalence of diabetes has risen exponentially and is projected to reach around 700 million by 2045[1]. DM is a metabolic disease, involving inappropriately elevated glucose levels and categories as two major subtypes, the type 1 (T1D) and T2D. diabetes. Patients with defective insulin secretion are considered to have T1D, and they typically present in their childhood or as adolescents. Contrarily, T2D affects middle-aged and older adults who have prolonged hyperglycaemia due to poor lifestyle and dietary choices[2]. T2D accounts for more than 90% of all type of DM, globally and is characterised by insulin resistance and insufficiency[3]. DM is also a major cause of morbidity and mortality in Hong Kong, in addition to being the 11th most common cause of deaths locally[4]. Even though T2D has traditionally be associated with middle and late adulthood, there has been an increasing number of cases reported in children, adolescents, and young adults over the last few years, driven by obesity and poor diet, raising a serious public health concern[3].

One of the reason behind this concern stems from the fact that early-onset of T2D is associated with a more severe disease phenotype, characterised by faster decline in beta-cells (β-cells) of pancreas, leading to necessitation of insulin therapy much earlier, alongside with an increased lifetime risk of developing unfavourable long-term outcomes[3]. More worryingly, early-onset of T2D is associated with an estimated median 7 years of life lost in those with a diagnosis between the age of 21 and 40 years compared to those without diabetes[5]. The seriousness of early-onset of T2D was reported in an epidemiologic study by Misra *et al*., (2022) who reported seeing a substantial number of individuals under the age of 40 with early-onset of T2D from most deprived areas of England. Furthermore, most of these individuals were less to attain the guideline recommended levels of glycated haemoglobin (HbA1c) due to inadequate care[5]. The local diabetic landscape is not significantly better since many insulin dependent diabetics under the age of 40 in Hong Kong are only provided continuous glucose monitoring (CGM) devices for a limited period of time, unlike other nations such as the United Kingdom where personal CGM is provided to all T1D and some T2D patients who are insulin dependent, according to a report by the Chinese University of Hong Kong (CUHK). Furthermore, the high cost of CGM ($1,000-$3,000+ Hong Kong Dollars [HKD] per month) is also one of the limiting factors in diabetic management, particularly for underprivileged socioeconomic groups[6].

A median 7 years of life lost in those with early-onset T2D...

A Partner in Crime: Cocoa and Diabetes

The primary goal in the management of diabetes is to achieve as near normal regulation of blood glucose as possible. Thus, both the type and total amount of carbohydrates (CHO) consumed influences the glycaemia[7]. Various clinical studies have demonstrated the potential of natural flavonoids in managing diabetes[8]. In addition, regular cocoa consumption (up to 100 g of chocolate or 54g of cocoa) has shown to improve blood pressure (BP), insulin sensitivity, and lipid levels in patients with T2D. These findings were explored in a double-blinded randomised, placebo-controlled trial by Dicks *et al*., (2018) which included 42 hypertensive patients with T2D (stable pharmacological treatment, with good adjustment for glucose metabolism, lipids, and BP). Patients were randomised to capsules with 2.5 g/day of a flavanol-rich cocoa or cocoa-free capsules for 12 weeks. Participants were expected to maintain diet, lifestyle and medications. The results showed that cocoa treatment did not affect BP, nor glucose metabolism (glucose, HbA1c, insulin, Homeostatic Model Assessment for Insulin Resistance [HOMA-IR]) and lipids (triglycerides, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]). Body weight, fat mass and nutrient supply remained unchanged when compared to placebo. Therefore, the study found no correlation between cocoa intake and improvement in cardiometabolic parameters[9].

Contarily, a systematic review and meta-analysis by Chen *et al*., (2022) indicated that cocoa products confers a positive effect of LDL-C, triglyceride, blood glucose, and C-reactive protein (CRP) in long-term. Furthermore, it also indicated that there are beneficial effects of cocoa products intake on cardiometabolic biomarkers for T2D, especially on blood glucose, lipid metabolism (LDL-C and triglycerides) and inflammation (CRP)[10]. These findings were further supported by a more recent study performed by Lin *et al*., (2024) that explored the relationship between different types of chocolate (dark, and milk chocolates), as well as total chocolate consumption with risk of T2D development. Remarkably, 18,862 individuals with incidental T2D were identified during the 829,175-person year of follow-up. After adjusting the personal, lifestyle, and dietary risk factors, participants consuming ≥ 5 servings/week of any chocolate showed a 10% (95% confidence interval [CI] 2% to 17%; P trend=0.07) lower rate of developing T2D compared with those who never or rarely consumed chocolate. Interestingly, participants who consumed ≥5 servings/week of dark chocolate

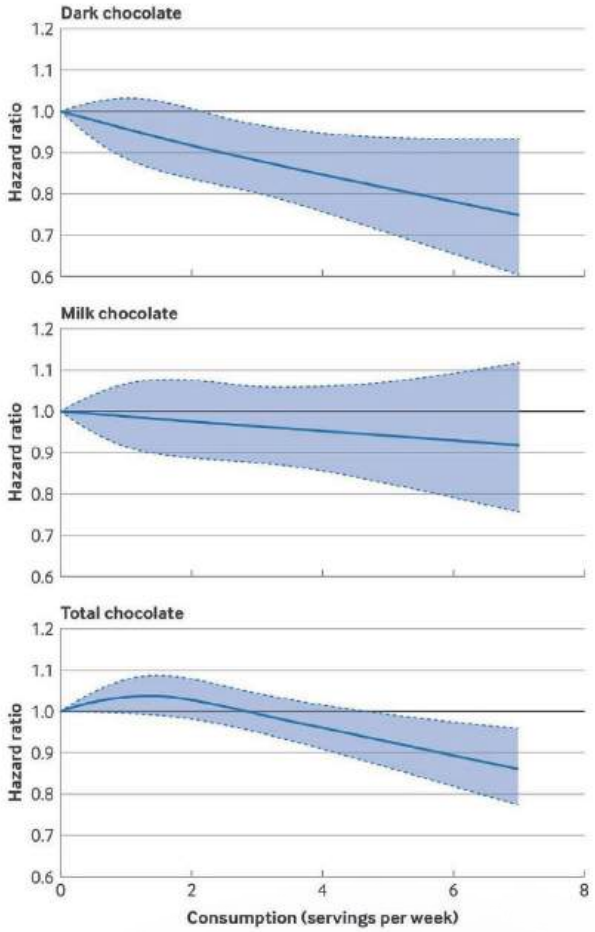

Figure 1: *Multivariable adjusted, pooled, dose-response associations between chocolate intake and risk of type 2 diabetes in NHS, NHSII, and HPFS1. NHS=Nurses' Health Study; NHSII=Nurses' Health Study II; HPFS=Health Professionals Follow-up Study; MET-h=metabolic equivalent tasks per hour*

showed a staggering 21% (5% to 34%; P trend=0.006) lower risk of developing T2D; however, no such reduction was found in participants who consume milk chocolate. These demonstrated that dark chocolate consumption correlated to a lower risk of T2D, whereas milk chocolate consumption correlated to weight gain only[1]. Nonetheless, these findings are still preliminary and more long-term trials are necessary to confirm the relationship between dark chocolate consumption and T2D. However, individuals are strongly recommended to maintain a healthy lifestyle that consists of a balance diet, and exercise. In conclusion, T2D prevention remains a public health concerns and healthcare providers should take an active role in prevention of T2D by promoting a healthier life choices for their patients.

Dark chocolate consumption may correlate to a lower risk of developing T2D, however, it is equally important to maintain a healthy lifestyle...

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www.vpulsehk.com

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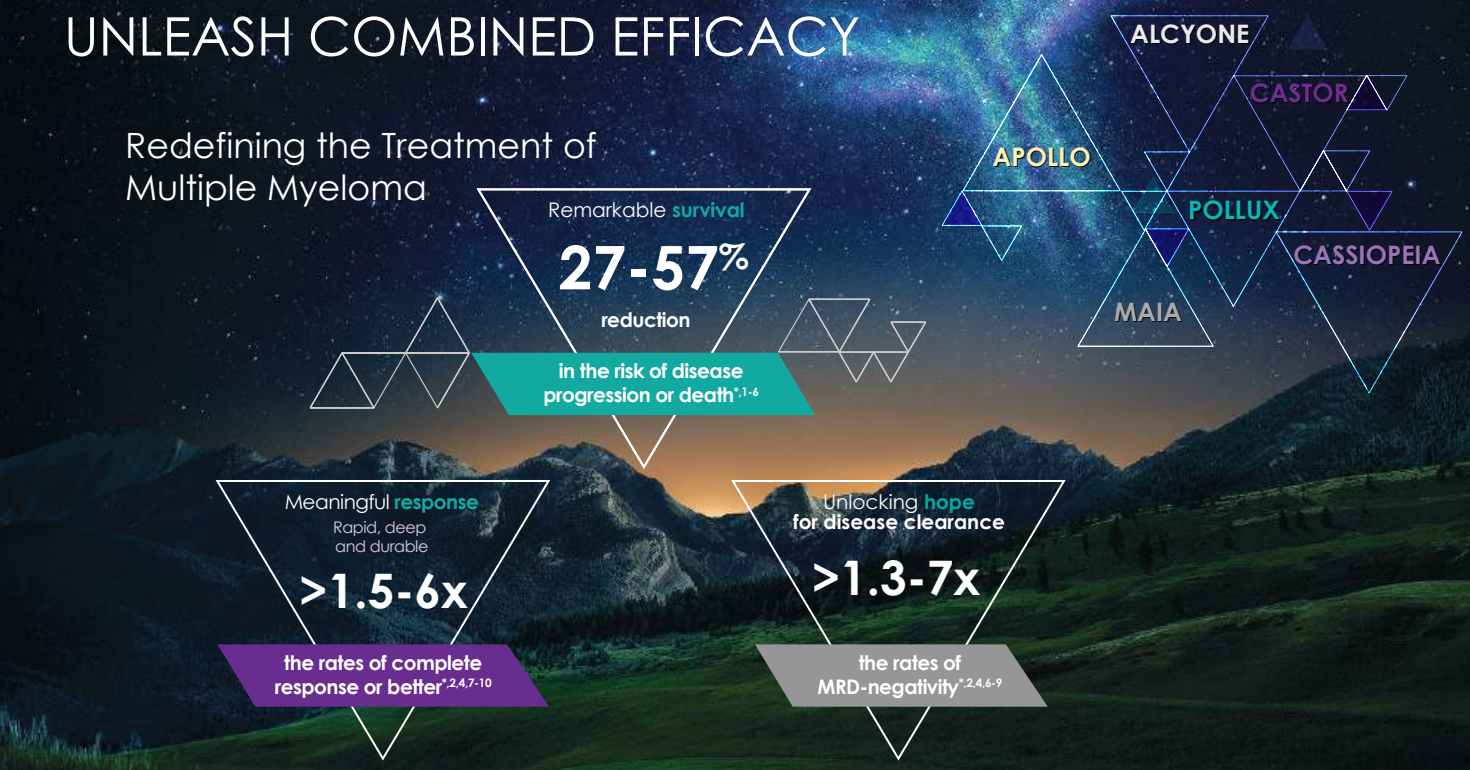
TRANSCEND THE BOUNDARY

UNLEASH COMBINED EFFICACY

Redefining the Treatment of Multiple Myeloma



Remarkable **survival**

27-57%

reduction

in the risk of disease progression or death*[1-6]

Meaningful **response**

Rapid, deep and durable

>1.5-6x

the rates of complete response or better*[2,4,7-10]

Unlocking **hope** for disease clearance

>1.3-7x

the rates of MRD-negativity*[2,4,6-9]

- AE profile consistent with regimen components, without new safety signals identified [11,12]
- Low rates of discontinuation due to AEs, and manageable IRRs [11,12]

Indications in MM

- **DARZALEX®** (daratumumab) in combination with lenalidomide + dexamethasone, or with bortezomib, melphalan and prednisone, is indicated for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- **DARZALEX®** in combination with bortezomib, thalidomide and dexamethasone, is indicated for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- **DARZALEX®** in combination with lenalidomide + dexamethasone, or bortezomib + dexamethasone, is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- **DARZALEX®** in combination with pomalidomide + dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy. (Subcutaneous formulation only)
- **DARZALEX®** as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
- See **DARZALEX®** prescribing information for full indication.[13,14]

* ALCYONE - DARZALEX® + bortezomib/melphalan/prednisone vs. bortezomib/melphalan/prednisone (for NDMM); APOLLO - DARZALEX® + pomalidomide/dexamethasone vs. pomalidomide/dexamethasone (for RRMM); CASSIOPEIA - DARZALEX® + bortezomib/thalidomide/dexamethasone vs. bortezomib/thalidomide/dexamethasone (for NDMM); CASTOR - DARZALEX® + bortezomib/dexamethasone vs. bortezomib/dexamethasone (for RRMM); MAIA - DARZALEX® + lenalidomide/dexamethasone vs. lenalidomide/dexamethasone (for NDMM); POLLUX - DARZALEX® + lenalidomide/dexamethasone vs. lenalidomide/dexamethasone (for RRMM)
AE = adverse event. IRR = infusion-related reaction. MM = multiple myeloma. MRD = minimal residual disease. NDMM = newly diagnosed multiple myeloma. RRMM = relapsed/refractory multiple myeloma.

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DARZALEX SOLUTION FOR SUBCUTANEOUS INJECTION 1800MG/15ML
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): Daratumumab
INDICATION(S): Multiple myeloma: 1) DARZALEX is indicated in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; 2) in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant; 3) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy; 4) in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy; 5) as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. Light chain (AL) amyloidosis: DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.
DOSAGE & ADMINISTRATION: 1800 mg administered subcutaneously over approximately 3-5 minute according to the dosing schedule in package insert. Refer to package insert for dose and schedule of other medicinal products in combination and recommended concomitant medicinal products.
CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients.
SPECIAL WARNINGS & PRECAUTIONS: Infusion-related reactions: patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs; Neutropenia/thrombocytopenia: complete blood cell counts should be monitored periodically during treatment; Interference with indirect antiglobulin test (indirect Coombs test): Interference with determination of complete response; Hepatitis B virus (HBV) reactivation: HBV screening should be performed in all patients before initiation of treatment.
SIDE EFFECTS: Infusion-related reactions, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Refer to the full prescribing information for other side effects.
PREGNANCY & LACTATION: DARZALEX is not recommended during pregnancy and in women of childbearing potential not using contraception. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
INTERACTIONS: No interaction studies have been performed.
PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.
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Darzalex® Concentrate for Solution for Infusion 100mg/5mL 400mg/20mL
ABBREVIATED PRESCRIBING INFORMATION
ACTIVE INGREDIENT(S): daratumumab
INDICATION(S): DARZALEX is indicated:
• in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
• in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
• in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
• as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
DOSAGE & ADMINISTRATION: Intravenous (IV) infusion only following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. DARZALEX dosing schedule - In combination with lenalidomide (4-week cycle regimen) and dexamethasone (Rd) and for monotherapy: 16 mg/kg body weight given weekly from weeks 1 to weeks 8, then every 2 weeks from weeks 9 to 24 and every 4 weeks from week 25 onwards until disease progression. In combination with bortezomib, melphalan and prednisone (6-week cycle dosing regimen): 16 mg/kg body weight, given weekly from weeks 1 to week 6, and then every 3 weeks for week 7 to 54 and every 4 weeks from week 55 onwards until disease progression. Bortezomib is given twice weekly at weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by once weekly at weeks 1, 2, 4 and 5 for eight more 6-week cycles. In combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT): 16 mg/kg body weight given weekly for induction from weeks 1 – 8, followed by every 2 weeks from weeks 9 – 16, and stop for high dose chemotherapy and ASCT. For consolidation, every 2 weeks from weeks 1 to 8. In combination with bortezomib and dexamethasone (3-week cycle regimen): 16 mg/kg body weight, given once a week for the first 9 weeks. From week 10 to 24, DARZALEX is given every 3 weeks, and then every 4 weeks from week 25 onwards until disease progression. Pre- and post-infusion medicinal products should be administered to reduce the risk of infusion-related reactions. To facilitate administration, the first prescribed 16 mg/kg dose at week 1 may be split over two consecutive days i.e. 8 mg/kg on day 1 and day 2 respectively.
CONTRAINDICATIONS: Known hypersensitivity to the active substance or to any of the excipients in the DARZALEX formulation.
SPECIAL WARNINGS & PRECAUTIONS: Infusion-related reactions (IRRs): DARZALEX can cause serious infusion related reactions (IRRs), including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported. Monitor all patients throughout the infusion for IRRs. Monitor post-infusion until symptoms resolve for patients experience any Grade IRRs. Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior treatment. Reduce infusion rate when re-starting infusion for patients with grade 1, 2 or 3 IRRs. If anaphylactic reaction or life-threatening (Grade 4) infusion reaction occurs, initiate appropriate emergency resuscitation immediately and discontinue DARZALEX therapy immediately and permanently. Neutropenia/thrombocytopenia: DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment and monitor patients with neutropenia for signs of infection. Interference with indirect antiglobulin test (indirect Coombs test): Daratumumab binds to CD38 found at low levels on red blood cells and may result in a positive indirect Coombs test. Patients should be typed and screened prior to starting daratumumab treatment. In event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests. Interference with determination of complete response: Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis and immunofixation assays used for clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein. Hepatitis B virus (HBV) reactivation: Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment. For patients with evidence of positive HBV serology, monitor signs of HBV reactivation during, and for at least six months following the end of treatment. In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Excipients: Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This corresponds to 0.46% and 1.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult, respectively.
SIDE EFFECTS: Most frequent adverse reactions: IRR, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions: sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.
Refer to the full prescribing information for other side effects.
PREGNANCY & LACTATION: Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment. Daratumumab is not recommended during pregnancy and in women of childbearing potential not using contraception. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from DARZALEX therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
INTERACTIONS: Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes. Interference with indirect antiglobulin test (indirect Coombs test): Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol to disrupt daratumumab binding or other locally validated methods or consider phenotyping/genotyping. Interference with serum protein electrophoresis and immunofixation tests: consider using validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum for suspected daratumumab interference.
PLEASE REFER TO FULL PRESCRIBING INFORMATION BEFORE PRESCRIBING.
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DARZALEX® SC daratumumab subcutaneous

DARZALEX® daratumumab concentrate for solution for infusion

by Dr. Mohsin Roshan

Unravelling the Intricate Connection Between Dentine Hypersensitivity and Gastroesophageal Reflux Disease

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BDS, MDS, PhD, FCDSHK, FHKAM
- *Tam Wah-Ching Professor in Dental Science*
- *Professor, Chair of Dental Public Health*
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Gastroesophageal reflux disease (GERD) is a chronic gastrointestinal (GI) disorder characterised by the regurgitation of gastric contents into the esophagus[1]. It is one of the most commonly diagnosed digestive disorder[1] with a global prevalence of 783.95 million in 2019[2]. Remarkably, around 5-10% of local population in Hong Kong reported experiencing acid reflux weekly[3]. Although, the reported incidence of GERD is much lower in the Chinese population compared to Caucasians[4], the prevalence of GERD has steadily been increasing in Asian over the last few years and rates are beginning to approach those reported in Western countries[5]. Notably, the risk factors for GERD include obesity, poor dietary habits, consumption of excessive alcohol, pregnancy, drug-induced, cigarette smoking, and stress[1,3]. Patient with GERD often complain of experiencing post-prandial burning sensation in the retrosternal area and acid regurgitation[6]. As the condition progresses, patient may experience a number of complications including erosive esophagitis, esophageal ulcers, strictures, and Barett's metaplasia[3]. Not surprisingly, GERD is also associated with a significant economic impact as it affects individual's quality of life (QoL)[7]. Currently, there are no gold standard for diagnosing GERD, thus diagnosis is often based on combination of presenting symptoms, endoscopic evaluation of the esophageal mucosa, reflux monitoring, and response to therapeutic intervention (8-week trial of empiric proton pump inhibitor [PPI] once daily before meal)[8]. GERD is a risk factor of dental erosion (DE)[9]. Stomach acid in GERD rises through the esophagus into the oral cavity, causing enamel erosion also named as DE, which leads to dentine hypersensitivity (DH)[10]. According to Picos *et al*., the prevalence of DE in GERD patients was higher as compared to control group (48.8% and 20.5%)[9]. According to the meta-analysis of Jordao et al., a 4.1-fold increased probability of DE in individuals with objectively measured GERD (pooled OR 4.1, 95% CI: 1.7–10.1) and a 2.7-fold in individuals with subjectively measured GERD/S, when compared to controls (pooled OR 2.7, 95% CI: 1.1–6.4) were recorded[9].

DE is defined as tooth surface loss caused by chemical or electrochemical processes of non-bacterial origin[11]. DH is defined as a short, sharp pain that arises from exposed dentin in response to non-noxious stimuli, typically thermal, evaporative, tactile, osmotic or

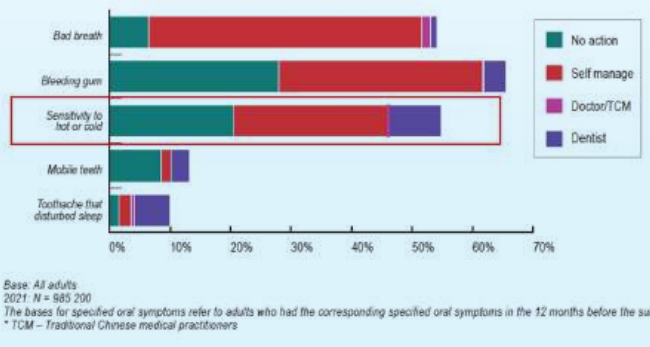

Figure 1: Proportion of adults according to the oral symptoms experienced (dental sensitivity marked in red box) in the 12 months before the survey and the action taken in 2021[14].

chemical, and that cannot be ascribed to any other form of dental defect or disease[12]. One commonly accepted theory is hydrodynamic theory, which suggests that changes in the fluid flow in dentinal tubules can trigger pain receptors present on nerve endings located at the pulpal aspect to fire nerve impulses, thereby eliciting pain[12]. There are various clinical conditions thought to play a role in the development of DH including DE, enamel attrition, and abrasion. Aggressive tooth brushing can also lead to the exposure of dentin, which ultimately leads to the development of DH[11]. Globally, 1 in 3 people may suffer from DH, peaking at 30 to 40 years old[13]. Locally, according to the oral health survey 2021 conducted by the Department of Health of Hong Kong SAR government, around 55% of individuals aged 35-44 had experienced dental sensitivity within a year and most of them either did not take any action or managed the oral symptoms by themselves rather than attending dental consultation (**Figure 1**)[14]. Two thirds (67.7%) of Hong Kong patients with periodontal condition had DH problem[15]. The vast majority (92%) of Hong Kong adults aged 25-45 years reported at least one symptom related to DE[11]. Understandably, people affected by DH often report its substantial impact on their daily lives when eating, drinking or even brushing[16]. More severe DH can last for more than 6 months and become consistently annoying, inducing psychological and emotional distractions[9].

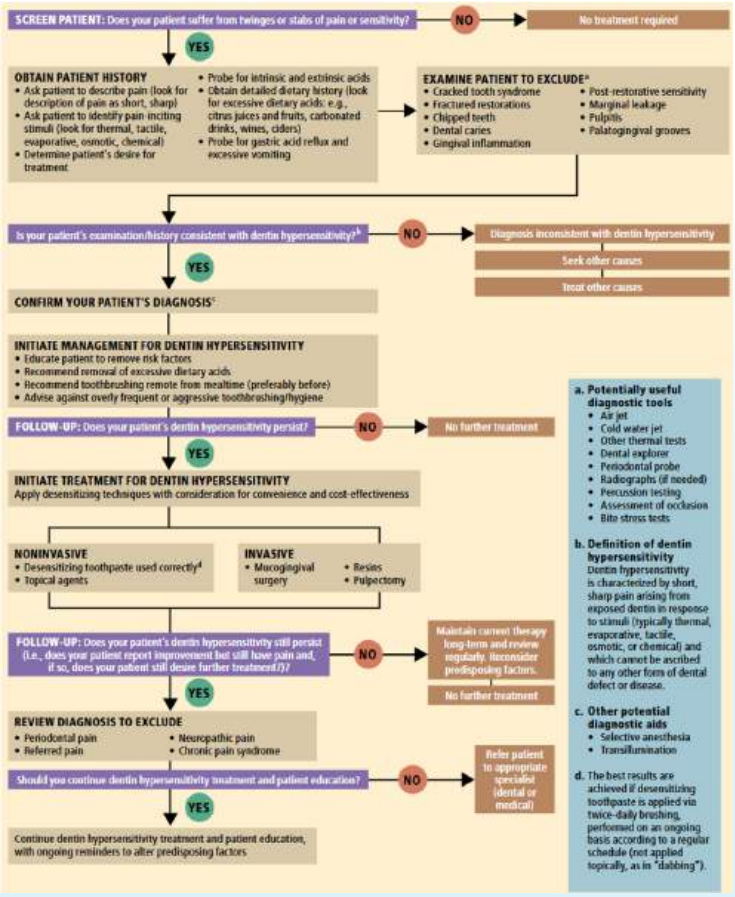

Figure 2: Algorithm for diagnosis and management of dentin hypersensitivity[12]

Unmasking the Detrimental Effects of Dentine Hypersensitivity

DE occurs by dissolving mineralized tooth tissues when exposed to non-bacterial acid. One of the factors that predispose individuals to DE is GERD due to chronic regurgitation of gastric contents to the oropharynx. Thus, individuals with GERD may have DE lesions as extraesophageal manifestations[17]. Of note, the upper incisors' palatal surfaces are initially attacked by refluxed acid, as the situation persists, the occlusal surfaces of posterior teeth in both arches erode. Similarly, the lower teeth are initially shielded by the tongue, but as the disease persists, the occlusal and buccal surfaces of these teeth eventually deteriorate[18]. Relentless exposure to pH below 5 will cause hydroxyapatite crystal in the dental enamel to dissolve and the tooth may have a yellowish tint due to tooth thinning, in addition to becoming overly sensitive to external stimuli[18]. A cross-sectional study by Ali et al. (2024) reported that individuals with DE who consumed more packaged food, pickles, soft drinks and sweets had a higher risk of DE[19].

Since DE often causes dentin exposure which invariable leads to the development of DH, the repercussion of the disease can be detrimental to patient's well-being. It is important to note that DH is always provoked subsequent to the delivery of an external stimulus, and rarely if ever present as pain that is either continuous or spontaneous[9]. The sequela of DH becomes apparent as the condition merits a serious burden on the individual's psychosocial and financial life[20]. Furthermore, DH can also alter the way patients act, restricting their eating habits, cause them to make adaptations to daily life and affect their social interactions as well as having emotional impact and affecting their personal identity[21]. In order to capture the nuances of DH's impact on QoL, the Dentin Hypersensitivity Experience Questionnaire (DHEQ) was developed to evaluate responsiveness to change in oral health-related QoL measures in DH patients[22,23]. Interestingly, research utilizing the DHEQ has found that among patients with DH, the adaptive behaviours fall into 4 categories: avoid, adapt, compromise and tolerate[24]. However, patients should not only be dependent on adaptive behavioural change. Instead, dental professional should openly discuss issues related to DH and offer treatment option during dental consultations[16].

Empowering Patients to Overcome Dentine Hypersensitivity

Treatment of DH is based on a thorough medical and dental history together with a clinical examination leading to a definitive diagnosis based on these findings. Detailed DH diagnosis and management guideline

can be found in **Figure 2**[12]. Effective treatment and controlling DH remain an important issue for dentists[25]. Strategies for management of DH include oral hygiene education, behavioural control and elimination of predisposing factors for DH, in addition to non-invasive treatment for pain relief[9]. In this context, toothpastes have been used in the treatment of DH since it is an easy, non-invasive, and most comprehensive way to treat hypersensitivity[26]. The best results are achieved if desensitizing toothpaste is applied via twice-daily brushing[12]. Notably, the primary aim here is to reduce the fluid flow in dentin tubules or block the nerve response in the pulp using various ingredients in desensitizing toothpastes, including potassium nitrate, stannous fluoride, arginine, and calcium sodium phosphosilicate (NovaMin). The mechanisms applied in tooth desensitizing are mainly by two pathways: nerve desensitization and tubule occlusion[12,25]. Each ingredient used in these desensitizing toothpastes is discussed as follows:

Potassium Nitrate (KNO_3)

KNO_3 has been incorporated into desensitizing toothpastes to reduce nerve excitation. This then increases the concentration of potassium ions, which is believed to decrease the excitability of the nerve against the action of sodium ions[27]. The efficacy of toothpaste containing KNO_3 was evaluated in a study by Pradeep *et al*. (2012) that included 149 subjects (72 males and 77 females; aged 20 to 60 years) randomly divided into 4 groups: Group 1- toothpaste containing 5% KNO_3; Group 2- toothpaste containing 5% calcium sodium phosphosilicate with fused silica; Group 3- toothpaste containing 3.85% amine fluoride; and Group 4- a placebo toothpaste. After sensitivity scores for controlled air stimulus and cold water at baseline were recorded, subjects were given toothpaste and sensitivity scores were measured again at 2 and 6 weeks. Group 1 toothpaste with 5% KNO_3 showed significant reduction in all sensitivity scores at weeks 2 and 6. The percentage decrease from baseline for the 5% KNO_3 dentifrice at week 6 was 57.1% and 54.4% in air and water stimulus, respectively. The comparison between test group with 5% KNO_3 and negative control group was also significant[28].

Stannous Fluoride (SnF_2)

SnF_2 is a scientifically recognized ingredient to strengthen enamel, relieve DH and protect gums[29-31]. SnF_2-based toothpaste works by forming an insoluble metal compound that precipitates into the dentin tubules to reduce dentin permeability to the stimuli[32]. In a randomized, examiner-blind, parallel, two treatment group, 8-week clinical study that compared the efficacy of an anhydrous dentifrice containing 0.454% weight to weight (w/w) stannous fluoride and a negative control dentifrice containing 1,000 parts per million (ppm) fluoride, as 0.76% w/w sodium monofluorophosphate, at reducing DH over 8 weeks with twice-daily brushing was evaluated. The study included 119 healthy subjects with at least two sensitive teeth, and 113 participants completed the study. Remarkably, at 4 and 8 weeks, between treatment analyses found that 0.454% w/w stannous fluoride dentifrice was significantly better than the negative control dentifrice in relieving DH for all measures (Schiff: p<0.0001 at 4 and 8 weeks; Visual Analogue Score [VAS] score: p=0.0003 at 4 weeks, p<0.0001 at 8 weeks; tactile threshold: p=0.0138 at 4 weeks, p<0.0001 at 8 weeks). At week 8, there was statistically significant decrease in adjusted mean Schiff sensitivity score from baseline for both the test (p<0.0001) and the negative control (p=0.0475 at week 8) (**Figure 3**)[33]. Noticeably, the percentage decrease from the baseline for the test dentifrice was 65.5% at week 8, with respective figure for the negative control of 7.4%[33].

NovaMin

NovaMin, also known as calcium sodium phosphosilicate has shown to bind to the collagen fibers in the exposed dentin, acting as a reservoir of minerals such as phosphate and calcium, forming a robust and repairing layer similar to hydroxyapatite on the exposed dentin tubules. Furthermore, the instantaneous contact of the components in an aqueous medium with saliva promotes the release of calcium and phosphate, forming an insoluble remineralizing hydroxyapatite carbonate on the enamel surface[26]. NovaMin is a highly water-reactive phosphosilicate consisting of fine powder particles that can physically obstruct dentin tubules and also demonstrate broad clinical efficiency in the enamel remineralisation process. These findings were substantiated in a double-blinded, parallel group randomized clinical study that compared the clinical efficacy of two commercially available toothpastes containing either 5% w/w NovaMin or 10% w/w

Time point	Statistics#	Test dentifrice (n=57)	Negative control dentifrice (n=57)	Treatment comparison*
Week 4	Adjusted mean (95% CI)	-0.98 (-1.11, -0.84)	-0.17 (-0.30, -0.03)	-0.81 (-1.00, -0.62)
	P-value	<0.0001	0.0189	<0.0001
Week 8	Adjusted mean (95% CI)	-1.46 (-1.63, -1.30)	-0.17 (-0.33, 0.00)	-1.29 (-1.53, -1.06)
	P-value	<0.0001	0.0475	<0.0001

*Figure 3: Summary of 4- and 8-week change from baseline Schiff sensitivity scores for the ITT population (n=114). #From ANCOVA model: Treatment as fixed factor, baseline Schiff sensitivity score as a covariate. *Difference is test dentifrice minus negative control dentifrice such that a negative difference favors test dentrifice[33]. CI, confidence interval; ITT, intention-to-treat.*

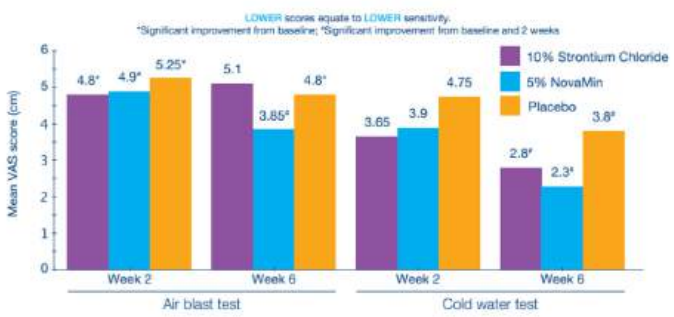

Figure 4: After 6 weeks of twice daily brushing use, NovaMin resulted in greater reduction in sensitivity (air and cold-water tests) than the placebo and 10% strontium chloride toothpaste[34].

strontium chloride and a matched placebo control toothpaste on DH. Remarkably, after the evaluation period, it was observed that after stimulation with a blast of air, 58% of subjects treated with NovaMin reported improvement in sensitivity, compared to only 26% of the group treated with 10% strontium chloride toothpaste and 20% with placebo (**Figure 4**)[34]. The results obtained demonstrated that the toothpaste containing NovaMin was more effective in reducing sensitivity compared to a commercial dentifrice and a placebo control. NovaMin can also enable the fill up of irregularities on enamel surface and thereby prevent erosion from acidic exposure. In addition, the eroded surface defects can be remineralised by providing calcium and phosphate and thereby reduce the mineral loss[35].

Arginine

Arginine is an essential amino acid with an alkaline pH, and its dentin-desensitizing effect in combination with calcium carbonate (as a rich source of calcium ions) has been proven in previous studies. Since both arginine and calcium ions are positively charged at physiological pH (alkaline by bicarbonate buffer), they are able to bind to negatively charged dentin surface and create a calcium-rich layer[36]. The effect of arginine-containing desensitizing toothpaste on DH was evaluated in a meta-analysis by Yang *et al*. (2016). In the analysis, 18 RCTs with 1,423 patients were included and the results demonstrated that at days 0, and 3; weeks 2, 4, and 8; and more than 12 weeks, arginine-containing toothpaste led to significantly improved results on tactile sensitivity test (standardized mean difference [SMD] =1.95, 95% confidence interval [CI] [1.14, 2.76]) and the air-blast test (SMD =−1.60, 95% CI [−2.14, −1.05]) at 4 weeks and the tactile sensitivity test (SMD =2.01, 95% CI [1.41, 2.61]) and the air-blast test (SMD =−1.41, 95% CI [−1.83, −0.98]) at 8 weeks compared to toothpastes containing other desensitizing components, thus indicating a superior therapeutic effect of arginine-containing desensitizing toothpaste. However, no significant differences between arginine-containing toothpaste and toothpastes containing other desensitizing components were observed in the air-blast test at days 0 and 3 and week 2 and in the tactile sensitivity and air-blast tests at more than 12 weeks[37].

Systematic reviews and meta-analysis have proven efficacy and QoL improvement of desensitizing agents such as KNO_3, stannous fluoride, arginine and NovaMin[29,35,38–41]. Although patients can simply use desensitizing toothpastes in their daily oral hygiene practices, clinical advice may help provide better maintenance for DH prevention and management. For instance, using soft-bristle toothbrush, applying 1,350-1,500 ppm fluoride toothpaste daily for adults, and expectorating excess toothpaste instead of rinsing with water straight after brushing to let the active ingredients to continue functioning. Furthermore, by simply avoiding toothbrushing immediately after meal, and avoid having in-office bleaching or using at-home bleaching tooth-whitening products such as carbamide peroxide and hydrogen peroxide, individuals can reduce their risk of DH[12,42]. Fluoride plays a pivotal role in enamel remineralization to combat against DE and tooth decay. Thus, it is important that the toothpaste has fluoride[42]. For patients who are keen to prevent both DH and tooth stain problems, they should use a single fluoride toothpaste that provides all the benefits including dental densensitization, non-bleaching whitening and enamel safe. In summary, toothbrushing with desensitizing toothpaste is recommended for preventing and treating both the DE and DH, which should be considered as a management tool in GERD patients.

Collaborative Approach to Prevention of DH in GERD Patients

DH is a widespread condition and over 70% of sufferers consider the sensations to take pleasure out of eating and drinking[43]. Moreover, DH carries a significantly negative effect on a person's oral health-related QoL since it has detrimental effect on their financial,

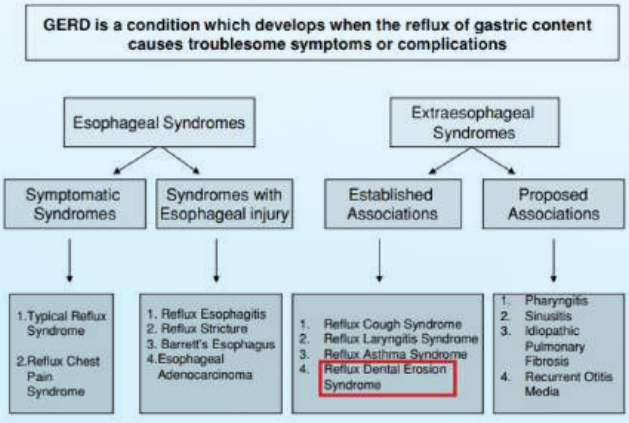

Figure 5: The Montreal classification of GERD. Text highlighted in red box indicates extraesophageal manifestations of the disease[45]. GERD, gastroesophageal reflux disease.

personal and social lives. Erosion of enamel driven by gastric reflux disease or ingestion of acidic substance has been identified as trigger or exacerbators of DH[44]. It is now believed that DE and GERD are related[18] and DE is considered an extraesophageal symptom as per the Montreal classification of GERD (**Figure 5**)[45]. Furthermore, GERD management nowadays has increasingly taken a multidisciplinary approach involving both the gastroenterologist and dentists[45]. Since acid reflux from the gastric environment often causes the salivary pH to fall and this represents an indisputable risk factor for DE. Thus, dental examination should be recommended for diagnosed and suspected GERD patients[46].

Despite of the important correlations between the two conditions, some clinicians still fail to appropriately diagnose patients with DE due to the heavily reliance on direct clinical observation which is considered an unreliable method for monitoring the rate of tooth wear by some[47]. Additionally, it is also important to remember that GERD is an intrinsic cause of tooth erosion and leads to the loss of enamel and dentin. This tooth structure loss leads to instability of the occlusion as teeth passively erupt (alveolar compensation) to maintain occlusion[47]. Thus, the intricate relationship between two conditions can only be managed through a holistic approach. Strikingly, dentist is often the first health care professional to diagnose systemic diseases through observations of oral manifestation and in case of GERD, DE and DH may be evident[48]. Dentist can help in early diagnosis of patients who have unexplained dental erosion and refer them to the gastroenterologist for further investigation. Collaboration effort between specialists during the diagnosing and managing of GERD would inevitably improve the patients' medical and dental health[49]. Equally, patient education is paramount since dentist play a pivotal role in maintaining patient's dental health (**Figure 6**). By simply making their patients aware of the repercussion related to acidic attack and irreversible dental damage, advice on potentially harmful drinks and food and about daily tooth brushing tips may make a difference to a patient's dental health and quality of life[12,48].

Suggestions for patients	Suggestions for dental professionals
Avoid using large amounts of toothpaste or reapplying it during brushing	Avoid overinstrumenting the root surfaces during scaling and root planing, particularly in the cervical area of the tooth
Avoid medium- or hard-bristle toothbrushes	Avoid overpolishing exposed dentin during stain removal
Avoid brushing teeth immediately after ingesting acidic foods	Avoid violating the biological width during restoration placement, as this can cause recession
Avoid brushing teeth with excessive pressure	Avoid burning the gingival tissues during in-office bleaching
Avoid excessive flossing or improper use of other interproximal cleaning devices	Advise patients to be careful when using at-home bleaching products
Avoid picking or scratching at the gingiva or using toothpicks inappropriately	

Figure 6: Recommendations to prevent dentine hypersensitivity[12]

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Self Study Questions (1 CME point):

1. According to the meta-analysis of Jordao *et al*., what was the increased probability of DE in individuals with objectively measured GERD?

A) 4.1-fold
B) 2.7-fold
C) 48.8%
D) 20.5%

2. Research utilizing the Dentin Hypersensitivity Experience Questionnaire (DHEQ) found among patients with DH, the adaptive behaviour falls into which of the following 4 categories?

A) Adapt, depress, compromise, tolerate
B) Stress, burnout, tolerate, adapt
C) Avoid, adapt, compromise and tolerate
D) Stress, avoid, compromise and adapt

3. Incorporation of potassium nitrate into desensitizing toothpaste functions to:

A) Increase nerve excitation and reduce potassium concentration.
B) Reduce the nerve excitation, and increase the concentration of potassium ions, and reduces excitability against the action of sodium ion.
C) Reduces the nerve excitation and propagates the action of sodium ion.
D) Reduces action potential of calcium ions.

4. Which of the following is/are preventive measure(s) against DH?

A) Avoid medium- or hard-bristle toothbrushes
B) Avoid brushing teeth immediately after ingesting acidic foods
C) Avoid in-office or at-home tooth bleaching
D) All the above

5. Summarising the whole article, how can frontline clinicians help improve patient's dental health and, hence, quality of life?

A) Enhancing the patient's awareness of the harmful impact of acidic attack on dental health.
B) Providing advice on food substances which may increase the risk of DE, and the appropriate way of tooth brushing.
C) Implementing the multidisciplinary approach involving dentists and gastroenterologists.
D) All the above.

This CME article was prepared by Professor Lo, Edward Chin Man and accredited by the Hong Kong Doctors Union (HKDU).

Please submit your answers via digital V.Pulse at vpulsehk.com or scan the QR code **on or before 20-March-2025**:

by Migee Tang

On-the-Pulse

Gynaecology

Probiotics against bacterial vaginosis – oral or vaginal route?[1-3]

Bacterial vaginosis (BV) is a vaginal infection commonly occurring in sexually active females due to imbalance in the vaginal microbiota. Despite treatment with antibiotics, recurrence rates can reach up to 50% within the initial 3 months post-treatment in BV[1]. As an alternative therapeutic approach, probiotics have recently been demonstrated to help improve vaginal microbiota and reduce relapses of BV, though the route of administration remains questionable. A study by Rezazadeh et al. compared treatment efficacy of probiotics in BV patients via oral vs. vaginal routes[2]. The reported findings suggest that both routes of administration were efficacious in reducing vaginal bacterial overgrowth, supporting the use of probiotics as a promising alternative to conventional antibiotic treatment. Lin et al. further revealed that different efficacies were observed with different probiotic strains[3]; thus, further research into the area is warranted to counteract effects of BV through a more holistic approach.

Dermatology

Good Skin Greens[4-6]

Diet is widely recognized to have significant impacts on our skin. The skin microbiome (SM) is uniquely made up of bacteria, viruses, and fungi. This microbial ecosystem interacts with the host through a symbiotic relation and confers several health benefits. Furthermore, gut bacterial DNA has been discovered in the plasma of individuals with psoriasis[4], providing further evidence for this microbial interaction. Recent studies suggest that vegetable consumption improves acne[5]; while dairy products such as cow's milk with high casein content may promote insulin-like growth factor 1 (IGF-1) to cause acne flareups. Similarly, soy-based products with high isoflavones and phytoestrogens have been shown to reduce acne flareups since both compounds counteract sebum production driven by androgenic activities[6]. Nonetheless, dairy products form an important part of our daily diets, and moderate consumption with a vegetable-rich diet may help keep the skin in check and reduce reliance of pharmaceutical treatment for acne.

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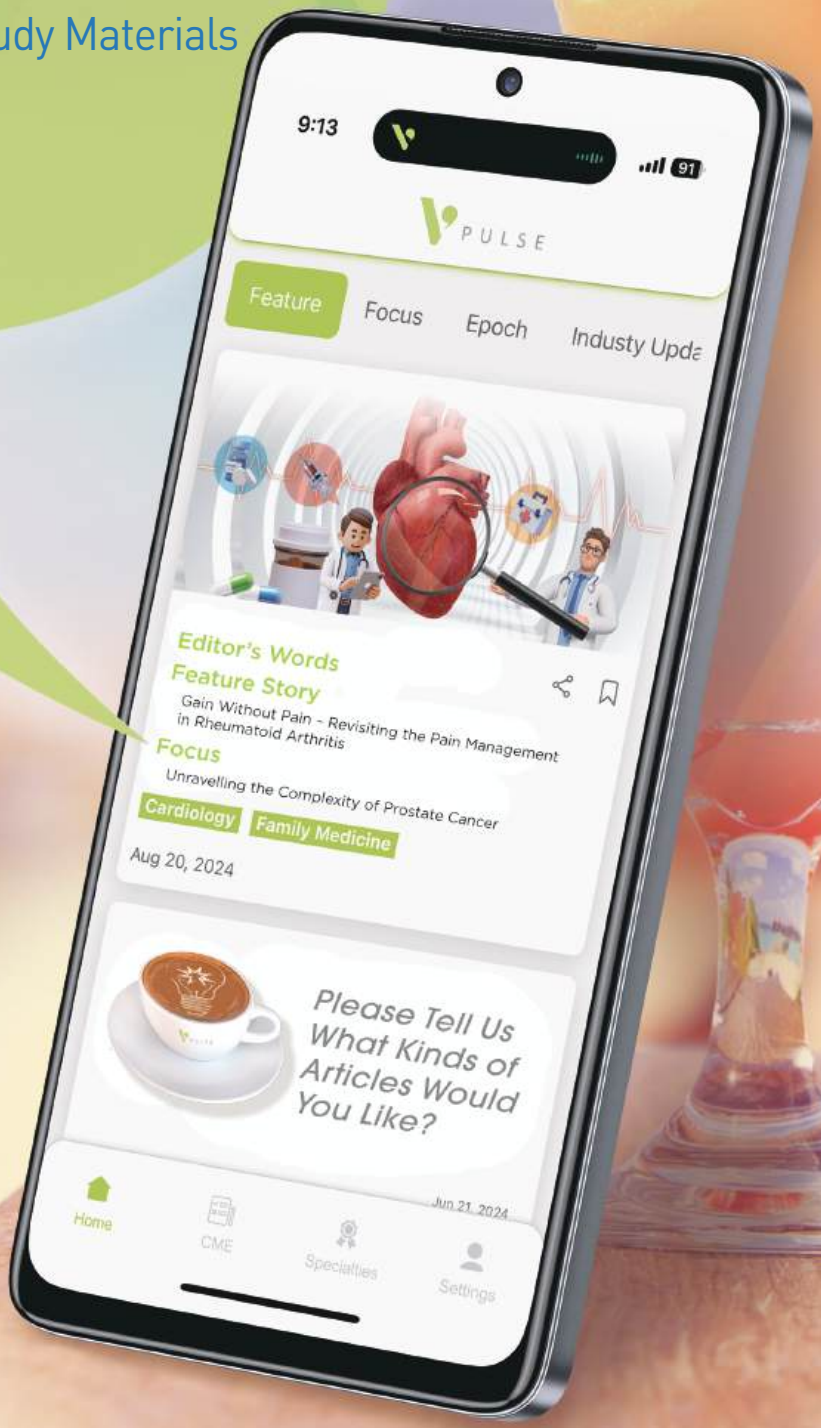

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Endocrinology

PHP-15 vs. Metformin: A Diabetes Showdown[7,8]

Up to 85.2% of type 2 diabetes mellitus (T2DM) patients are overweight or obese[7], which increases risks of comorbidities like fatty liver disease and insulin resistance. Metformin is the first-line treatment for T2DM and acts via the AMP-activated protein kinase (AMPK) pathway. Another compound, HPH-15, is also found to act on the AMPK pathway, hence proposed as an alternative treatment to metformin. Toma *et al*. investigated the glucose-lowering effects of HPH-15 in high-fat diet (HFD)-fed mice, which mimics physiological changes observed in diabetic patients[8]. Results showed significant reductions in random and fasting blood glucose, as well as insulin levels with 10 mg/kg and 100 mg/kg HPH-15 treatment to comparable levels as 300 mg/kg metformin. Insulin sensitivity increased to similar levels as metformin and liver lipid accumulation also decreased significantly, which addresses the crucial aspects of fatty liver disease and insulin resistance in diabetes management. HPH-15 also exhibited unique subcutaneous fat deposition reduction and antifibrotic effects in the liver. This study shows that HPH-15 has comparable and additional effects at much lower doses than metformin, highlighting its potential for patients with diabetes complicated by obesity and fatty liver.

Endocrinology

Regenerate with Harmine[9,10]

One of the hallmarks of diabetes is the reduction in number of functional, insulin-producing pancreatic beta cells[9]. Harmine, a dual tyrosine-regulated kinase 1A (DYRK1A) inhibitor, was recently shown to effectively combat this pathway. An increase of 300% in beta cell mass was observed in a human islet-grafted murine kidney model with harmine treatment alone, which further increased to 700% with an additional GLP-1 receptor agonist, exendin-4[10]. There was also improvement of beta cell function, including enhanced glucose-stimulated insulin secretion and rapid return to euglycemia[9]. A subsequent transcriptomics study revealed that harmine promoted transdifferentiation of cycling alpha cells into beta cells to cause this increase[9]. The utilization of patients' own alpha cell reservoir to produce new beta cells supports the scalability of the drug compared to current beta cell regenerative treatments like islet cell transplantations. Although further research to confirm translatability of study findings to humans is warranted, harmine demonstrates good potential as an affordable and scalable treatment for diabetes.

Oncology

Game Changer for Rectal Cancer[11,12]

While rectal cancer has favorable prognosis and high 5-year survival rates[11], treatment comes with significant complications like infertility and urinary dysfunction. A new anti-PD-1 monoclonal antibody, dostarlimab, has received FDA breakthrough therapy designation and shown promise as an organ-sparing treatment option. Cercek et al. evaluated the efficacy of dostarlimab in 16 mismatch repair-deficient stage II or III rectal cancer patients and found that 100% of participants who completed the 6-month treatment course achieved clinical complete response[12]. At 12-month follow-up, these patients remained progression and recurrence-free without the need for chemoradiotherapy or surgical resection. Adverse events resulting from treatment were also minimal. Though phase III studies in bigger patient groups are warranted, these findings strongly support the use of dostarlimab as a single-agent therapeutic option for mismatch-repair deficient rectal cancer patients. Its organ-sparing nature and reduced side effects compared to standard treatment may confer particular benefits to younger patients of childbearing age.

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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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400 mg/100 mg tablets

Psychiatry

Mind Games of Surveillance[13]

Altered behavioral patterns under self-perceived surveillance are well documented, such as increased tendencies to exhibit prosocial behaviors. Impacts of surveillance on more automatic aspects of cognition are less understood. Seymour et al. studied such psychological changes by evaluating individuals' ability to process facial stimuli. Facial perception was significantly faster when participants were watched, and when the shown facial image was one with direct gaze. This difference was not observed with non-facial stimuli. As facial information are important social cues, this suggests an increase in social-specific attentional bias. These findings provide interesting food for thought with increasing levels of social surveillance in today's society. Additional care should be considered towards mental health patients already exhibiting hypersensitivity to eye gaze due to irrational beliefs of being watched, such as those with psychosis or schizophrenia.

Nutrition

Intermittent Fasting – Friend or Foe?[14-16]

Intermittent fasting continues to gain popularity worldwide for its weight loss and other health benefits, including improvements in intestinal and muscular stem cell function[14,15]. Chen et al. studied for similar effects in hair and skin tissue regeneration but found contrary results to those hypothesized[16]. In intermittently-fasted shaved mice, only partial hair regrowth was seen after 96 days of study treatment compared to near-complete hair regrowth after 30 days in mice with unlimited food access. This is due to the activation of adrenal glands during extended durations of fasting which triggers fatty acid release, disrupting hair follicle stem cell (HFSC) metabolism and leading to apoptosis. Regeneration of HFSCs are hence halted and hair regrowth is inhibited. Nevertheless, it is unclear whether these results are translatable to humans due to the different metabolic rates of human and mice. Until larger clinical trials are conducted to confirm this, intermittent fasting can still be safely practiced for its wider health benefits.

Internal Medicine

Artificial Intelligence (AI) – New Guardian of Sleep Health[17]

The use of AI is becoming increasingly pronounced in our daily lives. Its potential in enha g sleep disorder diagnosis has recently been uncovered. Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is an early indicator for Parkinson's disease or dementia. Current diagnosis with a video-polysomnogram is deficient due to symptom overlap with other diseases and subjectivity of data from complex sleep variables. The newly enhanced AI algorithm detects rate, ratio, magnitude and velocity of movements, as well as ratio of immobility during REM sleep captured in video polysomnograms. An accuracy of up to 91.1% was achieved using this technology and demonstrates promising clinical potential in iRBD diagnosis. The ability of AI to automatically detect REM sleep also suggests its potential for use in home settings, offering a pathway to more accessible and widespread diagnosis for a condition that could otherwise easily go unnoticed.

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IN THE TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA, NINLARO® BRINGS[1]

Tourmaline MM1 study (n=722) was a double-blinded, placebo-controlled, phase 3 trial to compare efficacy and safety of Ixazomib(I), lenalidomide(R) & dexamethasone(d) vs placebo-Rd in relapsed/refractory multiple myeloma patients. The primary endpoint was progression free survival (PFS). The median PFS of IRd vs placebo-Rd was 20.6 months vs 14.7 months. The most common adverse events (>30%) included neutropenia, thrombocytopenia, diarrhea, rash and constipation.

NINLARO® in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

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Ninlaro 2.3mg, 3mg and 4mg Capsules

Presentation: Ixazomib 2.3 mg, 3 mg and 4 mg gelatin hard capsules. Indication: NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Dosage and administration: Recommended starting doses: NINLARO 4 mg (one capsule) administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle at least 1 hour before or at least 2 hours after food; lenalidomide 25 mg administered daily on Days 1 to 21 of a 28-day treatment cycle; dexamethasone 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle. Treatment should be continued until disease progression or unacceptable toxicity. Treatment with NINLARO in combination with lenalidomide and dexamethasone for longer than 24 cycles should be based on an individual benefit risk assessment, as the data on the tolerability and toxicity beyond 24 cycles are limited. Antiviral prophylaxis should be considered in patients being treated with NINLARO to decrease the risk of herpes zoster reactivation. No dose adjustment is necessary in patients over 65 years of age. Reduced 3 mg starting dose recommended in moderate or severe hepatic impairment. Reduced 3 mg starting dose recommended in severe renal impairment or end-stage renal disease requiring dialysis. Contraindications: Hypersensitivity to the active substance or to its excipients. As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the package insert for these medicinal products for additional contraindications. Warnings and precautions: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Platelet counts should be monitored at least monthly during NINLARO treatment. Thrombocytopenia can be managed with dose modifications and platelet transfusions as per standard medical guidelines. Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care. The dose should be adjusted for severe (Grade 3–4) symptoms. Patients experiencing new or worsening peripheral neuropathy may require dose modification. Patients with peripheral oedema should be evaluated for underlying causes and provided supportive care, as necessary. The dose of dexamethasone should be adjusted per its package insert or NINLARO for Grade 3 or 4 symptoms. Rash should be managed with supportive care or with dose modification if Grade 2 or higher. Stevens-Johnson syndrome (SJS) has also been reported with NINLARO. If SJS occurs, discontinue NINLARO. Cases of Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) have been reported in patients who received NINLARO. Some of these have been fatal. Signs and symptoms of TMA should be monitored for and NINLARO stopped if diagnosis is suspected. Hepatic enzymes should be monitored regularly and dose should be adjusted for Grade 3 or 4 symptoms. Pregnancy: Women should avoid becoming pregnant while being treated with NINLARO. In patients developing Posterior reversible encephalopathy syndrome (PRES), discontinue NINLARO. Interactions: Co-administration of strong CYP3A inducers with NINLARO is not recommended. No dose modification is required for NINLARO with co-administration of strong CYP3A inhibitors or strong CYP1A2 inhibitors. Women should avoid becoming pregnant while being treated with NINLARO. Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. Women using oral hormonal contraceptives should additionally use a barrier method of contraception. Breast feeding should be discontinued. Undesirable effects: Very common (all grades): Upper respiratory tract infection, bronchitis, thrombocytopenia, neutropenia, peripheral neuropathies, diarrhoea, constipation, nausea, vomiting, rash, back pain, oedema peripheral. Common (all grades): Herpes zoster. Serious adverse reactions: Serious adverse reactions reported in ≥2% of patients included diarrhoea (3%), thrombocytopenia (2%) and bronchitis (2%). As Ixazomib is administered in combination with lenalidomide and dexamethasone, refer to the package insert for these medicinal products for additional undesirable effects.

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Reference: 1. Moreau P et al. N Engl J Med. 2016 Apr 28;374(17):1621-1634.

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C-APROM/HK/NINL/0034 (03/2024)

by Michelle Lee

Innovative Approaches in Microbiome and Digital Health

Microbiome plays a pivotal role in human health, influencing key physiological functions such as digestion, immune system regulation, and mental well-being. Microbiome-based research and applications shed light on the significant impact of these microorganisms on human health and pave the way for personalized healthcare tailored to individual microbiome profiles. The growing recognition of the microbiome's importance has led to a rapidly expanding innovation market which reflects a global shift toward personalization and advancements in healthcare approaches, including healthcare service, medicine and digital health technology.

On the 11th January 2025, the Microbiome Summit 2025, themed "Microbes Spark Discovery" held at the Hong Kong Science and Technology Park, hosted by the Chinese University of Hong Kong and the Microbiota I-Center (MagIC), aimed to convene leading experts in cutting-edge microbiome research and applications for an exchange of ideas. This summit featured lectures and symposiums that focused on essential microbiomerelated topics, along with discussions on the microbiome innovation market.

Speaker:

Jan Knol

Professor of Microbiology, APC Microbiome Ireland and School of Microbiology, University College Cork

Early life nutrition is crucial for establishing a healthy gut microbiome, which in turn influences immune development, gut health, and long-term health outcomes for infants. Human milk is a complex liquid that has evolved as the optimal nutrition for sustaining healthy growth in infants. It provides essential nutrients and supports the development of a healthy microbiome. Milk fat globule (MFG) is one of the components of human milk, coated with a complex triple-layer MFG membrane (MFGM). Lipids are vital not only as a primary energy source but also for supporting the structural development and function of the immune system in infants and their later life.

Professor Jan Knol, a Professor of Microbiology at APC Microbiome Ireland and School of Microbiology at University College Cork, was invited to lead a keynote lecture on how early life nutrition affects the microbiome of infants. Prof. Knol emphasized that the gut microbiome is important, particularly in the early life of infants, and suggested that we can learn from the natural composition of human milk to improve infant formulas. Prof. Knol then shared a key innovation of

milk lipid globule, based on MFG, in infant formula. The large lipid globules found in infant formula are coated with phospholipid and mimic the lipid composition, structure and size of MFG. Notably, he shared studies that supported the health benefits of large lipid globules and suggested that infants fed with formulas containing large lipid globules can achieve healthy growth patterns closer to those of breast-fed infants, including the development of body mass index (BMI) and gut microbiome composition and function.

In summary, Prof. Knol highlighted that the innovative lipid globules in infant formula significantly contributed to enhancing its nutritional value, digestibility and overall health benefits, making it a more effective alternative to human breastmilk.

> ***Lipids are vital not only as a primary energy source but also for supporting the structural development and function of the immune system in infants and their later life.***

Speakers:

Jill Wong

Team Leader, Digital Health Innovation, Nutricia Research

Miller Guo

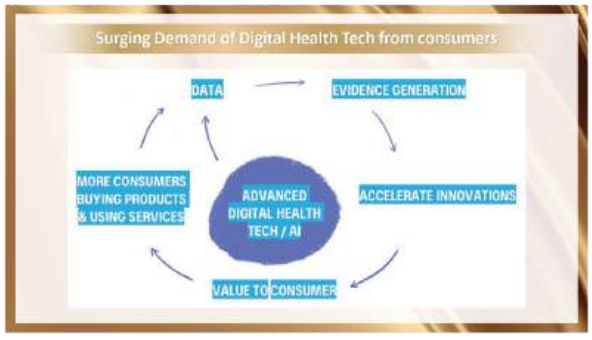
Head of Digital Health Tech, Danone Nutricia

Digital health is an innovative field that integrates technology into healthcare to enhance patient care and improve health outcomes through a wide range of tools. Along with advanced digital health technology and the expansion on artificial intelligence (AI) use, the healthcare landscape is rapidly transforming.

Jill Wong, team leader of Digital Health Innovation at D-Lab, Singapore, and Miller Guo, Head of Digital Health Tech at Shanghai Clinical Research Center (OSRC) in China, were invited to offer their view on AI digital innovation and digital health technology in the community.

Ms. Wong discussed the significant advancements in AI-powered digital health as she explained how AI enhances sophisticated analysis of vast amounts of data and facilitates personalized approaches in delivering healthcare services. Ms. Wong then shared her insights into the development of AI-powered tools and various examples of digital health tools that have been recently launched, such as Stool Tracker which utilize image recognition to help parents monitor their babies' microbiome, stool health and nutritional needs.

AI enhances sophisticated analysis of vast amounts of data and facilitates personalized approaches in delivering healthcare services.



Mr. Guo then divulged deeper into the realm of scientific digital health tech services. He discussed the transformative role of digital health technology in the development of digital health services. Together with AI, digital health technology empowers clinical studies and evidence generation by enhancing user engagement. Mr. Guo further explained how AI is utilized in Stool Tracker by analyzing and visualizing infants' microbiome and immunity with up to 96% accuracy against traditional methods. Additionally, Mr. Guo emphasized the importance of real-world evidence and consumer feedback in developing these services.

AI is utilized in Stool Tracker by analyzing and visualizing infants' microbiome and immunity with up to 96% accuracy against traditional methods.

Overall, both speakers illustrated how digital health innovations can transform and improve personalized nutrition and healthcare, in addition to user engagement. They emphasized their commitment to leveraging AI and digital health technology to enhance health outcomes for individuals and communities.

Scan here for more information

by Dr. Roy Lau

Hong Kong FemTech Start-up Launches HPV Detection Sanitary Pads

Cervical cancer is the 4th most common type of cancer in females globally, whereas over 99.7% of cervical cancers are due to persistent infection with genital type high-risk human papillomavirus (HPV). Notably, the estimated lifetime probability of acquiring HPV is unexpectedly high in both genders with 84.6% cases reported in females and 91.3% in males. Although most HPV subtypes are classified as low risk, the subtypes may cause benign diseases, such as genital warts. Given that most HPV infections are asymptomatic, diagnostic screening for HPV is thus a vital part of reducing risk of cervical cancer.

Conventionally, cytology test (Pap smear) has been the primary screening test for cervical cancer. However, a substantial proportion of women refuse taking the test, primarily due to the invasive procedure in collecting cells from the cervix and surrounding area. Besides, the subjective nature and relatively low sensitivity of Pap smear have prompted the development of better testing modalities with a higher accuracy.

Recently, WomenX, a local femtech start-up, has launched the non-invasive HPV testing sanitary pad ("PadX-HPV"), which is the first non-invasive method detecting 24 HPV subtypes directly from menstrual blood. The innovation offers a more accessible option for those uncomfortable with the traditional Pap smear tests. Essentially, a local study involving 119 Hong Kong female participants indicated that the sensitivity, specificity, and accuracy of PadX-HPV reached 100%, 98.9%, and 99.2%, respectively.

On 8-January-2025, a forum titled "Transforming Health: FemTech Against Cervical Cancer" was co-organised by WomenX and the Hong Kong Science and Technology Parks Corporation (HKSTP). During the event, leading experts from the health and technology sectors, including representatives from Mannings, Alliance Medical Group Holdings (AMG), EPlus Healthcare Centre (EPlus), FemTech Future, DEFTA Partners and etc. discussed the challenges and opportunities of self-testing products, focusing on increasing accessibility and credibility. Furthermore, the future of FemTech and the investment landscape was highlighted as well.

Dr. Choi Pui Wah, founder of WomenX, discussed the challenges and opportunities of self-testing products

Exhibition outlined the evolution of PadX-HPV

Guest participated in panel discussion

Participants from local health and technology sectors

Dr. Choi and leading experts from local health and technology sectors

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Indication[1]:

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- Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season

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  - Acute bacterial skin and skin structure infections (ABSSSI)
  - Community-acquired pneumonia (CAP)

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Indication[4]:

- Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy

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- 0% resistance detected at 5 years[1]
- No dosage adjustment for patients with eCrCl≥15mL/min or ESRD receiving chronic hemodialysis[4]

ALT: Alanine Aminotransferase CHB: Chronic Hepatitis B; eCrCl: Estimated Creatinine Clearance; ESRD: End Stage Renal Disease

*Comparison of ALT normalization, viral suppression, and impact on renal and bone function were made between tenofovir aladenamide and tenofovir disoproxil fumarate.[1-3]

Product photo shown is not actual size.
The person depicted is not an actual healthcare professional.

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3. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, noninferiority trial. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):185-195.
4. Vemlidy Prescribing Information. (Version HK-JUN22-US-SEP21).

VEMLIDY® Abbreviated Prescribing Information (Version: HK-JUN22-US-SEP21) Presentation: Tablets: 25 mg of tenofovir alafenamide - yellow, round, film-coated tablets, debossed with "GSI" on one side of the tablet and "25" on the other side. **Indications:** VEMLIDY is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease. **Dosage:** Prior to initiation of VEMLIDY, patients should be tested for HIV-1 infection. VEMLIDY alone should not be used in patients with HIV infection. Adults: The recommended dosage is 25 mg (one tablet) taken orally once daily with food. Patients with Renal Impairment: No dosage adjustment is required in patients with estimated creatinine clearance greater than or equal to 15 mL/min, or in patients with end stage renal disease (ESRD; estimated creatinine clearance below 15 mL/min) who are receiving chronic hemodialysis. On days of hemodialysis, administer VEMLIDY after completion of hemodialysis treatment. VEMLIDY is not recommended in patients with ESRD who are not receiving chronic hemodialysis. Patients with Hepatic Impairment: No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh A). Not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment. **Contraindications:** None. **Warnings and Precautions:** Severe acute exacerbation of Hepatitis B after discontinuation of treatment: Discontinuation of VEMLIDY, may result in severe acute exacerbations of hepatitis B. Patients who discontinue VEMLIDY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. Risk of development of HIV-1 resistance in patients coinfected with HBV and HIV-1: Due to the risk of development of HIV-1 resistance, VEMLIDY alone is not recommended for the treatment of HIV-1 infection. The safety and efficacy have not been established in patients coinfected with HBV and HIV-1. HIV antibody testing should be offered to all HBV-infected patients before initiating therapy with VEMLIDY, and, if positive, an appropriate antiretroviral combination regimen that is recommended for patients coinfected with HIV-1 should be used. New onset or worsening renal Impairment: Prior to or when initiating VEMLIDY, and during treatment with VEMLIDY on a clinically appropriate schedule, assess serum creatinine, estimated creatinine clearance, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue VEMLIDY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Lactic acidosis/severe hepatomegaly with steatosis: Treatment with VEMLIDY should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). **Adverse reactions:** Refer to warning and precautions for severe acute exacerbation of hepatitis B, new onset or worsening of renal impairment, and lactic acidosis/severe hepatomegaly with steatosis. Headache, abdominal pain, cough, back pain, fatigue, nausea, arthralgia, diarrhea and dyspepsia were reported in ≥ 5% of subjects in clinical studies. **Drug interactions:** Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Antimycobacterial: rifabutin, rifampin, rifapentine. Herbal Products: St. John's wort. Drugs that reduce renal function or compete for active tubular secretion such as acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. **Before prescribing, please consult full prescribing information which is available upon request.** VEMLIDY is a registered trademark of Gilead Sciences, Inc., or its related companies.

For medical enquiries, please send your request to asiamedinfo@gilead.com or call 800 908 348 (toll-free number).

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Vemlidy®
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