PULSE

Gain Without Pain – Revisiting the Pain Management in Rheumatoid Arthritis

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AML=acute myeloid leukemia; CI=confidence interval; HR=hazard ratio; OS=overall survival.

See below for study design of the QUAZAR AML-001 trial, which evaluated the efficacy and safety of ONUREG® vs placebo as maintenance therapy in patients with AML in first remission following induction therapy* with or without consolidation.

* Intensive induction Chemotherapy

ONUREG TABLETS 200MG
ONUREG TABLETS 300MG
ABBREVIATED PRESCRIBING INFORMATION

ACTIVE INGREDIENT: ONUREG (azacitidine) is supplied as film-coated tablets containing 200 mg or 300 mg of azacitidine for oral use.

INDICATIONS: ONUREG is indicated for continued treatment of adult patients with acute myeloid leukemia who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

DOSAGE AND ADMINISTRATION: The recommended dosage of ONUREG is 300 mg orally once daily with or without food on Days 1 through 14 of each 28-day cycle. Continue ONUREG until disease progression or unacceptable toxicity. Administer an antiemetic 30 minutes prior to each dose of ONUREG for the first 2 cycles. Antiemetic prophylaxis may be omitted after 2 cycles if there has been no nausea and vomiting. If the absolute neutrophil count (ANC) is less than 0.5 Gi/L on Day 1 of a cycle, do not administer ONUREG. Delay the start of the cycle until the ANC is 0.5 Gi/L or more. ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures. Monitor complete blood count every other week for the first 2 cycles and prior to the start of each cycle thereafter. Increase monitoring to every other week for the 2 cycles after any dose reduction for myelosuppression.

CONTRAINDICATIONS: ONUREG is contraindicated in patients with known severe hypersensitivity to azacitidine or its components.

WARNINGS AND PRECAUTIONS: Risks of Substitution with Other Azacitidine Products: Due to substantial differences in the pharmacokinetic parameters, the recommended dose and schedule for ONUREG are different from those for the intravenous or subcutaneous azacitidine products. Do not substitute ONUREG for intravenous or subcutaneous azacitidine. Myelosuppression: Monitor complete blood counts and modify the dosage as recommended. Provide standard supportive care, including hematopoietic growth factors, if myelosuppression occurs. Increased Early Mortality in Patients with Myelodysplastic Syndromes: The safety and effectiveness of ONUREG for treatment of myelodysplastic syndromes have not been established. Treatment of patients with myelodysplastic syndromes with ONUREG is not recommended outside of controlled trials. Embryo-Fetal Toxicity: Based on the mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose.

ADVERSE REACTIONS: Serious adverse reactions occurred in 15% of patients who received ONUREG. Serious adverse reactions in ≥ 2% of patients who received ONUREG were pneumonia (8%) and febrile neutropenia (7%). One fatal adverse reaction (sepsis) occurred in a patient who received ONUREG. Permanent discontinuation of ONUREG due to an adverse reaction occurred in 8% of patients. Adverse reactions which resulted in permanent discontinuation of ONUREG in > 1% of patients included nausea (2.1%), diarrhea (1.7%), and vomiting (1.3%). Interruptions of ONUREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required an interruption of ONUREG in > 5% of patients included neutropenia (20%), thrombocytopenia (8%), and nausea (6%). Dose reductions of ONUREG due to an adverse reaction occurred in 14% of patients. Adverse reactions which required a dose reduction in > 1% of patients included neutropenia (6%), diarrhea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%). The most common (≥ 10%) adverse reactions were nausea, vomiting, diarrhea, fatigue/asthenia, constipation, pneumonia, abdominal pain, arthralgia, decreased appetite, febrile neutropenia, dizziness, and pain in extremity. The following adverse reactions have been identified during postapproval use of intravenous or subcutaneous azacitidine: Hypersensitivity reaction, Interstitial lung disease, Tumor lysis syndrome, Sweet's syndrome (acute febrile neutrophilic dermatosis), Necrotizing fasciitis (including fatal cases), Differentiation syndrome.

USE IN SPECIFIC POPULATIONS: Pregnancy: Based on its mechanism of action and findings in animals, ONUREG can cause fetal harm when administered to a pregnant woman. There are no available data on ONUREG use in pregnant women to evaluate for a drug-associated risk. Advise pregnant women of the potential risk to the fetus. Lactation: There are no data regarding the presence of azacitidine in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with ONUREG and for 1 week after the last dose. Females and Males of Reproductive Potential: ONUREG can cause embryo-fetal harm when administered to pregnant women Pregnancy testing is recommended for females of reproductive potential before starting ONUREG. Advise females of reproductive potential to use effective contraception during treatment with ONUREG and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ONUREG and for at least 3 months after the last dose. Based on animal data, ONUREG may impair male or female fertility. Pediatric Use: The safety and effectiveness of ONUREG in pediatric patients have not been established. Geriatric Use: No overall differences in safety or effectiveness of ONUREG were observed between these patients and younger patients. Renal Impairment: Monitor patients with severe renal impairment more frequently for adverse reactions and modify the ONUREG dosage for adverse reactions. No dose adjustment of ONUREG is recommended for patients with mild to severe renal impairment. Hepatic Impairment: ONUREG has not been studied in patients with pre-existing severe hepatic impairment. A recommended dosage of ONUREG has not been established for patients with moderate hepatic impairment. No dose adjustment of ONUREG is recommended for patients with mild hepatic impairment.

DRUG INTERACTION STUDIES: Coadministration of omeprazole (a proton pump inhibitor) with ONUREG increased azacitidine AUC0-INF by 19% and had no effect on Cmax. Azacitidine does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP2E1 at clinically relevant concentrations. Azacitidine is not an inducer of CYP1A2, CYP2C19, or CYP3A. Azacitidine is not a substrate of P-glycoprotein (P-gp). Azacitidine does not inhibit P-gp, breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2 at clinically relevant concentrations.

Please refer to the full prescribing information before prescribing. Prescribing information is available on request.
Date of revision of the text: July 2023

Study design and survival outcomes: The efficacy of ONUREG® was evaluated in QUAZAR AML-001, a multicenter, randomized, double-blind, placebo-controlled, phase III study. Eligible patients were aged 55 years or older, had AML, and were within 4 months of achieving first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) with intensive induction chemotherapy with or without consolidation therapy. A total of 472 patients who were ineligible for hematopoietic stem cell transplant (HSCT) were randomized 1:1 to receive ONUREG® 300 mg (n=238) or placebo (n=234) orally on Days 1 to 14 of each 28-day treatment cycle. Efficacy was established on the basis of OS and relapse-free survival (RFS). The trial demonstrated a statistically significant improvement in OS for patients randomized to ONUREG® compared with placebo (24.7 months with ONUREG® vs 14.8 months with placebo; HR: 0.69 [95% CI: 0.55, 0.86] P=0.0009). RFS was also significantly improved with ONUREG® vs placebo (10.2 months vs 4.8 months, respectively; P<0.001).[1,2]

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EDITOR'S WORDS

Dear Reader,

The disease burden of rheumatoid arthritis (RA) is substantial, which adversely affects the patients, their families, and the healthcare system. Notably, RA-associated pain is often debilitating and have detrimental effect on patients' overall quality of life (QoL). In contrast to the early concepts, contemporary view considered pain as a complex set of neural, humoral, and emotional events. Hence, it is crucial to appreciate that not all RA-associated pain is affiliated to the active disease, whereas non-inflammatory pain has also been reported. In the current Feature Story, the pathophysiology and multifaceted impacts of RA-associated pain will be reviewed. Essentially, the recent advancement in pharmacological treatment against RA pain will be highlighted. In addition, the clinical performance of physical therapy and the roles of psychological intervention in the holistic care for RA patients will be discussed.

Apart from RA, prostate cancer (PCa) is a complex disease that affects millions of males globally. Importantly, PCa often follows an indolent clinical course since patients with PCa often remain asymptomatic during the early stages of the disease. Therefore, the disease is often diagnosed at late stages requiring extensive treatment. To uncover the complex nature of PCa, Prof. Ng Chi Fai, the Director of SH Ho Urology Centre at the Chinese University of Hong Kong (CUHK), was invited to discuss the underlying reasons for the late diagnosis of the disease. Moreover, Prof. Ng will also highlight the treatment in early and advanced stages of the disease. Particularly, the use of robot-assisted radical prostatectomy (RARP), and the integration of artificial intelligence (AI) in clinical practice will be featured.

In addition to the thematic topics, updates on the pharmacologic management multiple myeloma (MM), and the essence in optimising protein intake in patients with chronic kidney disease (CKD) are highlighted in the Industry Updates. On the other hand, updates in rabies preventive treatment, treatment for advanced glaucoma, and epidemiological issues about hepatocellular carcinoma (HCC), and recent trial data on repurposing pomalidomide in reducing hemorrhagic telangiectasia (HHT)-related epistaxis will be discussed in the Epoch section.

Hope you enjoy this issue!

Dr. Roy Yuen-chi Lau
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Editor-in-Chief

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Intended for Healthcare Professionals only.

Abbreviations: BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder.

References: **1.** Wu H, et al. Biol Psychiatry. 2021 Jun 1;89(11):1030-1032. **2.** Hayley S, et al. Front Cell Neurosci. 2013 Nov 20;7:218. **3.** Castrén E, et al. Biol Psychiatry. 2021 Jul 15;90(2):128-136. **4.** Bathina S, et al. Arch Med Sci. 2015 Dec 10;11(6):1164-78. **5.** Salahudeen MS, et al. Ther Adv Drug Saf. 2020 Jul 23;11:2042098620937899. **6.** Jamieson C, et al. Health Qual Life Outcomes. 2023 May 8;21(1):40. **7.** Canuso CM, et al. J Clin Psychopharmacol. 2021 Sep-Oct 01;41(5):516-524. **8.** Daly EJ, et al. JAMA Psychiatry. 2019;76(9):893-903. **9.** Zaki N, et al. Neuropsychopharmacology. 2023 Jul;48(8):1225-1233. **10.** SPRAVATO® Hong Kong Prescribing Information P03.

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by Dr. Roy Lau

Gain Without Pain – Revisiting the Pain Management in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease that initially affects small joints, and gradually involves larger joints with varying degree of severity. Apart from joint damage and bony erosion, pain is a common and often debilitating symptom reported by RA patients[1]. Essentially, RA-associated pain can be associated with psychological distress, and this may impair physical and social functioning, and increase healthcare utilisation. To counter RA-associated pain, a multimodal approach is taken that includes pharmaceutical agents, physical therapy, and patient education. Additionally, psychological interventions, such as cognitive behavioural therapy (CBT), has also shown to play an essential role in improving the well-being of RA patients in the setting of chronic or intermittent pain[2]. Thus, the aim of this article is to review the pathophysiology of RA-associated pain and to evaluate the clinical performance of current treatment against this phenomenon.

RA-associated Pain – A Common Yet Debilitating Symptom

Pain is often debilitating and have detrimental effect on individual's quality of life (QoL) across different aspects. The cross-sectional study by Vergne-Salle *et al*. (2020) reported 38.4% of 295 RA patients from 7 French rheumatology centres having a visual analogue scale (VAS) pain score greater than 40 mm/100 (**Figure 1**), though 83% of them were on biological treatment and 38.7% were in remission based on the RA activity score[3]. The findings thus highlighted that despite medications being prescribed, a substantial proportion of RA patients still experience relentless pain.

The Clinical Significance of Non-inflammatory Pain in RA

In contrast to the early concepts, which hypothesised pain intensity being directly related to the amount of tissue injury, the contemporary view considered pain as a complex set of neural, humoral, and emotional events that involve the release of noxious mediators, inflammation, peripheral and central sensitisation, as well as remodelling of synaptic contacts[4].

In the context of RA, persistent pain is a complex and multifactorial phenomenon attributable to peripheral inflammation and sensitisation, as well as central pain mechanisms with central sensitisation[3]. In particular, inflammation and degenerative processes are the primary causes of pain, while inflammatory pain is commonly triggered within the joints during periods of active disease. In this regard, pain is a critical determinant of RA treatment outcomes. Nonetheless, it is crucial to appreciate that not all RA-associated pain affiliated to the active disease, instead non-inflammatory pain has also been reported[5]. For instance, fibromyalgia (FM) is a common disorder reported among RA patients, with about 12-48% of RA patients reported to have concurrent FM. Interestingly, patients with FM often report widespread and chronic pain. Furthermore, they may also have a lower threshold for the painful stimuli[6].

Moreover, bone and cartilage destruction associated with RA may gradually lead to the development of secondary osteoarthritis, resulting in mechanical pain despite the patient having a disease remission or low disease activity. Although glucocorticoids (GCs) are often considered effective to alleviate inflammation and synovitis, long-term use of GCs has shown to be associated with numerous side effects, including infection, diabetes, hypertension, adrenal insufficiency, and osteoporosis. Additionally, GCs are also reported to indirectly contribute to non-inflammatory pain by causing changes in body habitus and mood disturbances[5].

Providing inflammation is not the sole cause of RA-associated pain, RA treatment traditionally aimed to decrease inflammation and achieving remission may not address the existing adverse impacts of RA has on patient's lives. In contrast, attention to non-inflammatory targets of pain management and psychosocial support is also paramount.

The Multifaceted Impacts of RA-associated Pain

According to the RA Impact of Disease (RAID) study (2009), which involved 96 patients from 10 European countries, pain was selected by the respondents as the most important domain to be included in the calculation of the RAID score, which is a patient-derived weighted score utilised to assess the impact of RA. The study suggested that pain was a concern in 21% of the respondents, followed by functional disability (16%), fatigue (15%), emotional well-being (12%), sleep (12%), coping (12%) and physical well-being (12%)[7].

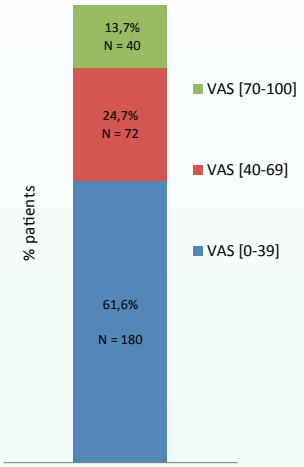

Figure 1. *VAS pain score reported by RA patients*[3]

It has been well-established that RA makes patients less independent and often interferes with their daily activities, such as working, participating in hobbies, and receiving support, thereby reducing their QoL. RA patients with more pain tend to experience loss of leisure-time activities. Not surprisingly, sexual dysfunction is also prevalent among RA patients since joint stiffness and fatigue may make it difficult for RA patients to engage in sexual activities[8], further worsen propounded by pain, which may then lead to a reduce libido[9], indirectly having negative impact on their QoL and relationships.

Of importance, RA-related disability causes a substantial loss of income to the individual and society at large. Birnbaum *et al*. (2010) estimated that the annual excess healthcare costs of RA patients mounted to around $8.4 billion, and costs of other RA-related issues around $10.9 billion in the United States (U.S.), whereas 33% of the total cost was allocated to employers, 28% to patients, 20% to the government, and 19% to caregivers (**Figure 2**). With the intangible costs of QoL deterioration and premature mortality, the total societal costs of RA were $39.2 billion (in 2005 dollars)[10].

More recently, an estimation of the economic burden of RA in the U.S. reported by Poudel *et al*. (2023) indicated that the average annual total direct cost per person of RA patients using disease-modifying antirheumatic drugs (DMARDs) has almost doubled ($24,729 to $45,867) from 2008-09 to 2018-19), while the expenditure on medications was a key driver for the increase in economic burden[11].

Mental impacts, pain, fatigue, and early morning stiffness (EMS) predominantly affect QoL in RA patients, as well as contribute to high disease activity and are likely to predispose RA patients to depression. Interestingly, cytokines, such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNFα), and interleukin 1 beta (IL-1β), are not only involved in the pathogenic mechanism of depression but also in pain and fatigue. In this regard, RA patients treated with anti-IL-6 disease-modifying antirheumatic drugs (DMARDs) show an improvement in pain and fatigue, with lower levels of depression[12].

Mood disorders, like depression and anxiety, have been incriminated as potential factors for relapse periods in RA patients, and they significantly alter the way patients perceive their current health. Notably, pain catastrophising is a psychological response characterised by an exaggerated

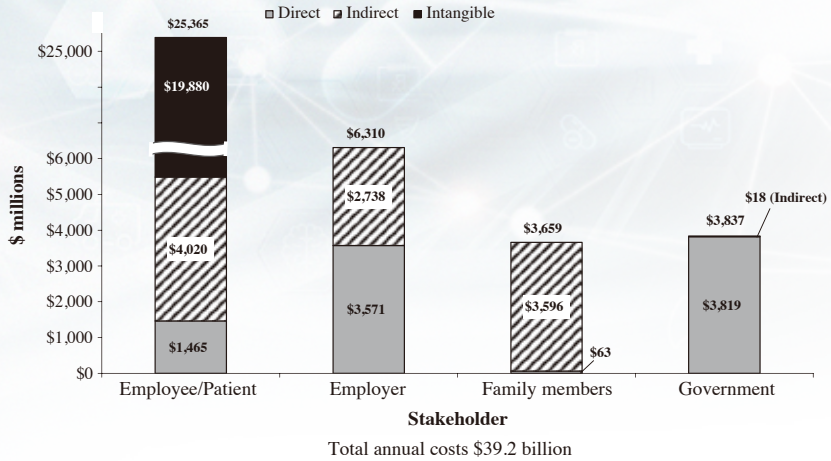

Figure 2. *Annual societal costs of RA ($ millions)*[10]

perception of the pain's threat. Patients suffering from the condition tend to anticipate the worst outcomes, ruminate on pain-related thoughts, and expect their pain to persist or intensify. Pain catastrophising has been suggested to increase distress and amplify pain sensitivity[13].

By virtue of the broad scope of adverse impacts of RA, holistic management has to be implemented for RA patients in addition to the treat-to-target pharmacological treatment for symptom control.

Pharmaceutical Interventions Against RA Pain

Given there is no cure for RA, the treatment goals often rely on reducing joint inflammation and pain, maximising joint function, and avoiding joint destruction and deformity[14]. According to the consensus recommendations addressed by the Hong Kong Society of Rheumatology (HKSR), methotrexate (MTX) should be the first-line therapy unless contraindicated, whereas leflunomide or sulfasalazine may be considered as initial conventional synthetic DMARD (csDMARD) therapy if MTX is contraindicated or not tolerated by the patient[15].

If no clinical response to the first csDMARD is observed in 3 months or the treatment target is not reached in 6 months, adjustment of DMARD therapy is indicated. Moreover, when the treatment target cannot be achieved with MTX or other csDMARDs, the add-on of biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) may be considered in the presence of poor prognostic factors of RA. Of note, the recommendation suggested that systemic GC as bridging therapy should be avoided when a new b/tsDMARD is initiated due to the increased risk of infection[15].

In the pharmacological management of RA pain, Janus kinase inhibitors (JAKi) have demonstrated promising efficacy in pain relief in previous clinical studies. For instance, the recent prospective cohort study by De Stefano *et al*. (2023), involving 181 RA patients initiated on JAKi therapy, demonstrated that the proportion of patients who achieved ≥30%, ≥50% and ≥70% pain improvement (VAS pain score) at 24 weeks was 61.4%, 49.3% and 32.9%, respectively (**Figure 3**). Furthermore, 40.6% and 28.5% of the patients achieved thresholds of remaining pain equivalent to mild pain or no/limited pain. The results also reported that pain improvements were more evident in patients naive to previous biologics[16]. Based on these findings, JAKi was confirmed effective in relieving pain in RA patients.

The Roles of Physical Therapy in Controlling RA Pain

In addition to pharmacological treatment, physical modalities, such as therapeutic exercises, may help to improve strength, endurance, mobility, and pain relief, and thus are essential components of rehabilitation care for rheumatic disorders. Notably, many RA patients avoid performing physical activities due to the fear of worsening pain or pressure on joints, which leads to decreased muscle strength and, ultimately, disability. Therefore, encouraging RA patients to perform physical activities as appropriate remains vital.

The benefits of exercise therapy in improving outcomes and pain relief in RA patients are well-established. A recent meta-analysis of 13 randomised controlled trials (RCTs), accounting for 967 RA patients, by Ye *et al*. (2022) indicated that aerobic exercise significantly improved functional ability (mean difference [MD]: −0.25, p=0.0002), increased aerobic capacity (MD: 2.41, p<0.00001) and improved the Sit-to-Stand test score (MD: 1.60, p=0.04). Importantly, the results further indicated that the pain score obtained from the aerobic exercise group was significantly lower than that of the control group (standard mean difference [SMD]: −0.46, p=0.04, **Figure 4**)[17].

Apart from physical exercises, manipulation has been shown to decrease joint pain and normalise function. Nonetheless, the exact mechanism of action of this treatment remains elusive, though it has been postulated to relieve pain by correcting muscle imbalance. Besides, stretching techniques are also advocated to increase flexibility, reduce the risk of injury, as well as relieve joint and myofascial pain[18].

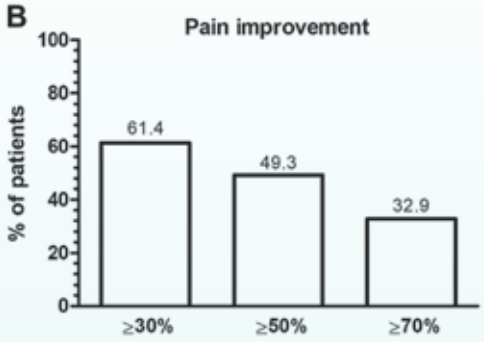

Figure 3. *Percentage of patients who achieved pain relief thresholds with JAK inhibitor treatment*[16]

While heat and cold therapies, with thermal packs or water baths, are commonly used physical modalities for improving joint flexibility and pain relief, electrical stimulation of the nerves, muscles, or both has been considered for the pain management as well. By passing direct current (DC) across the painful area, both nociceptors and slow fibres that mediate pain are suppressed. Practically, transcutaneous electrical nerve stimulation (TENS) has gained popularity since the devices are portable[18].

As a complex spectrum of musculoskeletal conditions is involved in RA, managing RA pain obviously requires the physiotherapeutic approach alongside pharmacological treatment. Thanks to the continuous research and development of integrative approaches in RA management, diverse physical therapy modalities have emerged as a cornerstone in alleviating pain and restoring daily function for patients.

Psychological Intervention and Patient Education

Provided the impacts of RA are often multidimensional, the holistic approach to the disease undoubtedly has to take both physiological and psychosocial aspects into account. Notably, there are numerous clinical data confirming psychological therapy as efficacious for RA patients in improving both physical and psychological functioning. More specifically, cognitive behavioural therapy (CBT) has ushered a new era by becoming the most efficacious treatment for pain management in RA[2].

Practically, the pain and functional disability module of CBT for RA patients may consist of progressive relaxation, attention diversion, stimulation of physical exercising in daily life in the face of the current physical condition, activity pacing, problem-solving, adjustment of goal setting, identification of pain-provoking cues in daily life, and cognitive restructuring of dysfunctional pain cognitions[19]. Ultimately, CBT helps patients develop a more realistic and balanced attitudes toward their disease.

A recent randomised controlled trial (RCT) by Omidvar *et al*. (2024), which included 36 RA patients, demonstrated that individuals receiving 8-sessions of CBT (n=21) had their pain self-efficacy scores significantly improved compared to the control group (n=15, Pain Self-Efficacy Questionnaire [PSEQ] score at follow-up: 35.62 [CBT] vs. 14.23 [control], p <0.001)[20].

Besides CBT, patient education is also an intervention aimed to assist RA patients to strengthen their life and health management. Previous studies suggested that educational interventions can increase RA patients' disease awareness and treatment options, thereby improving their adherence to treatment[21]. Remarkably, a recent meta-analysis of 24 RCTs on patient education for RA by Wu *et al*. (2022) evaluated the effectiveness of patient education on psychological status and clinical outcomes in RA. The outcome measures in the study included pain, physical function, disease activity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anxiety, depression, arthritis self-efficacy (ASE), and general health[22].

The results revealed a statistically significant overall effect in favour of patient education for physical function, disease activity, ASE (pain, other symptoms, and total), and general health. Health education for RA patients may have a positive impact on the perception of pain and the disease management. Active participation in educational interventions facilitate the transformation of knowledge about disease and methods of preventing pain into changes in health behaviour. This results not only in pain relief and reduced disability but also in the improvement in body function[22].

The Holistic Care for RA Patients

This article briefly reviewed the adverse impacts of RA and the associated pain on patients and society. Furthermore, to restrict the disease burden, a holistic approach, including pharmacological treatments, physical therapies, psychological interventions, and patient education, is often required. When considering the ultimate goal of RA management, the wellness practices proposed by Taylor and co-workers (2021) is undeniably noteworthy. Wellness can be regarded as a multi-dimensional, holistic concept encompassing lifestyle, environment, mental and spiritual well-being. At the same time, wellness practices often include exercise, optimised sleep, optimised nutrition, mindfulness, social connectedness, and positive emotions[23]. Optimising these aspects may help RA patients to improve their overall health status. Thus, it is desirable to consider wellness practices in addition to treat-to-target pharmacological agents for the holistic management of RA patients.

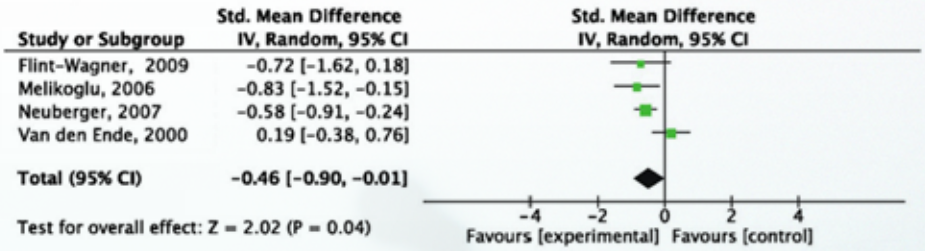

Figure 4. *Forest plot of influence of aerobic exercise interventions on pain score*[17]

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Self Study Questions (1 CME point):

1. Which of the following statement(s) about RA-associated pain is/are correct?

i. According to Vergne-Salle *et al*. (2020), 83% of RA patients on biological treatment reported a visual analogue scale (VAS) pain score greater than 40 mm/100
ii. The contemporary view considered pain intensity is directly related to the amount of tissue injury
iii. Inflammation and degenerative processes are the primary causes of pain in RA

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

2. Which of the following is/are the impact(s) of RA according to the RAID study?

i. Fatigue
ii. Sleep
iii. Sexual dysfunction

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

3. Which of the following statement about the consensus recommendations addressed by the Hong Kong Society of Rheumatology (HKSR) is correct?

A) Methotrexate (MTX) should always be the first-line therapy
B) Leflunomide or sulfasalazine may be considered as initial conventional synthetic DMARD therapy if MTX is contraindicated or not tolerated
C) Adjustment of DMARD therapy is indicated if the treatment target is not reached in 3 months
D) None of above

4. Which of the following about the meta-analysis by Ye *et al*. (2022) is correct?

A) 13 retrospective cohort trials were included
B) Aerobic exercise significantly improved functional ability, increased aerobic capacity, but not improved the Sit-to-Stand test score
C) The pain score obtained from the aerobic exercise group was significantly lower than that of the control group
D) The *p* value for the test of overall effect was <0.00001

5. Which of the following is/are consisted in the pain and functional disability module of CBT for RA patients?

i. Progressive relaxation
ii. Adjustment of goal setting
iii. Cognitive restructuring of dysfunctional pain cognitions

A) i 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).

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by Dr. Mohsin Roshan

Thriving Beyond the Challenges of Multiple Myeloma Post-Transplantation

Dr. Grace Lau

Specialist in Haematology and Haematological Oncology
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Multiple myeloma (MM) is a clonal plasma cell disorder characterised by excess production of monoclonal immunoglobulins and light chains that can ultimately lead to specific end-organ damage[1]. Notably, MM is the second most common haematologic malignancy and represents approximately 1% of all cancers[2]. Patients with symptomatic myeloma are often treated with a combination of active agents, and eligible patients then proceed to high-dose chemotherapy with autologous stem cell transplantation (ASCT). However, disease relapse invariably occurs post-ASCT. Therefore, different therapies have been employed post-transplantation as a maintenance treatment to improve progression-free survival (PFS) and overall survival (OS)[3]. Thus, to understand the role of maintenance treatment post-ASCT, we have invited Dr. Grace Lau, a specialist in Haematology and Haematological Oncology to share her expertise on the ever-changing treatment landscape of MM through a case-based sharing.

Decoding the Enigma of Multiple Myeloma

MM accounts for 1% of all cancers and approximately 10% of all haematologic malignancies[4]. The exact aetiology of MM is unknown[5]. Chronic antigenic stimulation from infection, chronic inflammation[6] and exposure to toxic substances (for instance, alcohol, insecticides) and radiation has been associated with an increased incidence of plasma cell myeloma[7]. Furthermore, emerging studies have also suggested that obesity is associated with an increased risk of developing MM and may worsen the outcome for these patients; however, the causal relationship is not established[8].

MM is a disease of the elderly and its incidence increases with age. It is postulated that with the aging population, nearly 3 out of every 4 patients diagnosed with myeloma will be aged ≥ 65[9]. Dr. Lau explained that apart from the aging population, MM is also more common in males than females[10]. She added that the racial and ethnic disparities is prevalent in MM, with non-Hispanic Black individuals being twice as likely to be diagnosed with MM compared with non-Hispanic White individuals[11]. Fortunately, over the last 10-20 years, the introduction of novel therapies has resulted in a deeper and more durable treatment responses in MM patients, resulting in long-term disease control with hope for a cure in the future[12]. Dr. Lau added that the change has been revolutionary with the availability of agents such as anti-CD38 monoclonal antibodies[13], proteosome inhibitors and immunomodulatory drugs such as lenalidomide[14]. Furthermore, the betterment of supportive care further reduces the risk of MM-induced

complications and treatment-related adverse events[15], according to Dr. Lau. For instance, the use of bone modifying agents has been shown to substantially reduce bone pain and skeletal events[16]. Vaccination, appropriate antimicrobial prophylaxis and the use of intravenous immunoglobulin markedly decrease the risk of infection in these immunocompromised patients[17]. It is of paramount importance to regularly review the patient's tolerability of the treatment since supportive care and dosing modification can effectively minimise treatment-related side effects, according to Dr. Lau.

Diagnostic Dilemmas in Multiple Myeloma

Considering the symptoms of MM being vague and non-specific, early detection of the disease poses a serious diagnostic challenge in the primary care[18]. Dr. Lau elucidated that the diagnosis of MM requires ≥10% clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytoma plus any of the myeloma-defining events, commonly known as CRAB which includes hypercalcaemia, renal failure, anaemia, or bony lesions, attributable to the underlying plasma cell disorder. Other myeloma-defining biomarkers include bone marrow clonal plasmacytosis ≥60%, serum involved/uninvolved free light chain (FLC) ratio ≥100 (provided involved FLC is ≥100 mg/L) and >1 focal lesion on magnetic resonance imaging[4], which are "associated with roughly 80% probability of progression to MM within 2 years when present," according to Dr. Lau. She stated that the prognosis of patients newly diagnosed with MM (NDMM) relies on the molecular profile of the disease, along with other clinical risk factors, such as raised lactate dehydrogenase (LDH), elevated serum beta-2 microglobulin, hypoalbuminemia, primary refractory disease and extramedullary disease[19].

Dr. Lau elaborated that MM symptoms are highly non-specific[20], therefore, can be easily misdiagnosed as other medical conditions initially, leading to potential diagnostic delay. For instance, MM patients may first present with back pain and stiffness, which can easily be misattributed as arthritis[21]. Moreover, due to a lack of awareness of this condition in primary care, the attending physician may not immediately consider MM as a differential diagnosis, resulting in a delay in referring the patient for further investigations[22]. Additionally, differentiating various causes of vertebral collapse, based solely on X ray findings can be difficult and this can further contribute to a delay in diagnosis if appropriate follow-up examinations are not performed[23]. Thus, Dr. Lau advocated to seek specialist advice early if in doubt since this may help expedite the diagnosis and prompt the appropriate treatment for the patient.

Optimising Clinical Outcomes with Maintenance Treatment in MM

MM is incurable, and relapse is inevitable because of the residual disease[24]. Therefore, after ASCT, thalidomide maintenance therapy has often been implemented in the past since MM patients treated with thalidomide showed an improved PFS; however, due to treatment-emergent adverse events (TEAEs) such as peripheral neuropathy, it is often difficult for MM patients to remain on thalidomide maintenance regimen[24]. Dr. Lau pointed out that MM patients with high-risk deletion of 17p treated with thalidomide often showed no survival benefit in terms of the OS[25]. Contrary to this, lenalidomide seems to be a better option as a maintenance therapy due to better patient tolerance and improved PFS after ASCT in MM patients compared to placebo[26].

To illustrate the treatment benefits of lenalidomide, Dr. Lau shared the findings of a meta-analysis by McCarthy *et al*., (2017) with 1,208 intention-to-treat (ITT) population (605 NDMM patients in the lenalidomide maintenance group and 603 in the placebo or observation group). The median PFS (mPFS) was 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (hazard ratio [HR] 0.48; 95% confidence interval [CI]: 0.41-0.55) (**Figure 1**)[26]. Moreover, the cumulative incidence rate of progression or death as a result of myeloma was higher in the placebo or observation group compared to the lenalidomide maintenance group. The meta-analysis concluded that lenalidomide maintenance after ASCT in patients with NDMM demonstrated a significant OS benefit and PFS compared to placebo or observation[26]. Dr. Lau pointed out that MM patients at stage I and II of the international staging system (ISS) derive the most benefit with lenalidomide, compared to patients at stage III of the disease[26].

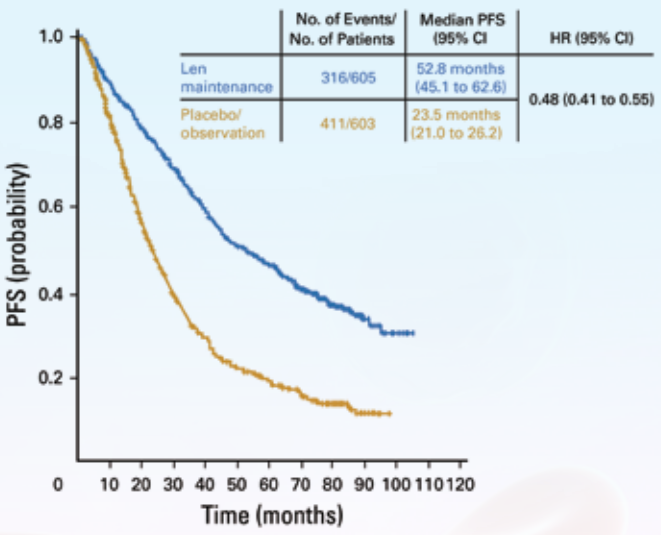

Figure 1. *Kaplan-Meier estimates of progression-free survival (PFS)[26]. CI= confidence interval; HR= hazard ratio; Len= lenalidomide*

Resilience of Lenalidomide in Real-World Clinical Practice

Lenalidomide has been approved as the first and only post-ASCT maintenance therapy since the 2017 after results from two phase III trials (IFM 2205-02 and CALGB 100104 trials) showed significant improvement in PFS, event-free survival and OS with lenalidomide maintenance compared to placebo[27]. Hence, to demonstrate its efficacy and safety in real-world clinical practice, Dr. Lau shared the case of a 59-year-old female who initially presented with generalised rib pain. Blood tests showed anaemia (haemoglobin [Hb] of 8.7g/dL), elevated levels of creatinine (180 umol/L) with hypercalcemia (3.32 mmol/L). Moreover, the skeletal survey revealed numerous lytic lesions over the ribs, cranial vault, pelvis, and the lumbar spine, in addition to fractured left 10th rib and partial collapse of T12 vertebra. Dr. Lau explained that the patient was eventually commenced on treatment after the diagnosis of MM and received 6 cycles of bortezomib, thalidomide and dexamethasone (VTd) from September 2012 to March 2013.

Remarkably, the patient was in complete remission (CR) only after receiving 2 cycles of VTd in November 2012 as indicated by the paraprotein levels in **Figure 2** and stringent CR (sCR) was attained after the 3rd treatment cycle with VTd by the December 2012. Subsequently, the patient underwent ASCT following induction with VTd and was commenced on lenalidomide 10 mg maintenance following the cell count recovery post-ASCT. Strikingly, the patient remained in sCR since 2012 and only had neutropenia which was managed through dose adjustment. These findings have also been substantiated in a retrospective single-center analysis of adult MM patients that received upfront ASCT between 2005 and 2021, followed by single-agent lenalidomide maintenance[28]. A total of 1,167 patients were included with a median age of 61.4 years, and median follow-up of 47.9 months[28]. Interestingly, the median PFS and OS for the entire cohort was 56.6 months (95% CI: 48.2-61.4) and 111.3 months (95% CI: 101.7-121.5). The study concluded that the outcome with lenalidomide maintenance was comparable to those reported in larger clinical trial and longer duration of maintenance, even beyond 5 years, was associated with improved survival[28].

Nevertheless, despite the therapeutic benefits of lenalidomide, the drug is not completely devoid of side effects. Haematological toxicity is common. Grade 3 or 4 neutropenia[29] can be managed with the use of G-CSF, dose interruption and dose modification[30]. Furthermore, rash can occur in up to one-thirds of the patients but is usually mild and rarely leads to treatment discontinuation[31]. Females of child-bearing potential and males should be advised to practise contraception because of the teratogenic potential of lenalidomide[32]. Notably, lenalidomide maintenance is associated with a slightly higher risk of secondary malignancy which warrants ongoing monitoring although the survival benefits outweigh risk[33]. With careful monitoring of these adverse events and appropriate interventions, majority of patients can be maintained on lenalidomide until the disease progression. In conclusion, lenalidomide is a stepping stone for keeping the disease at bay, representing the treatment revolution in MM.

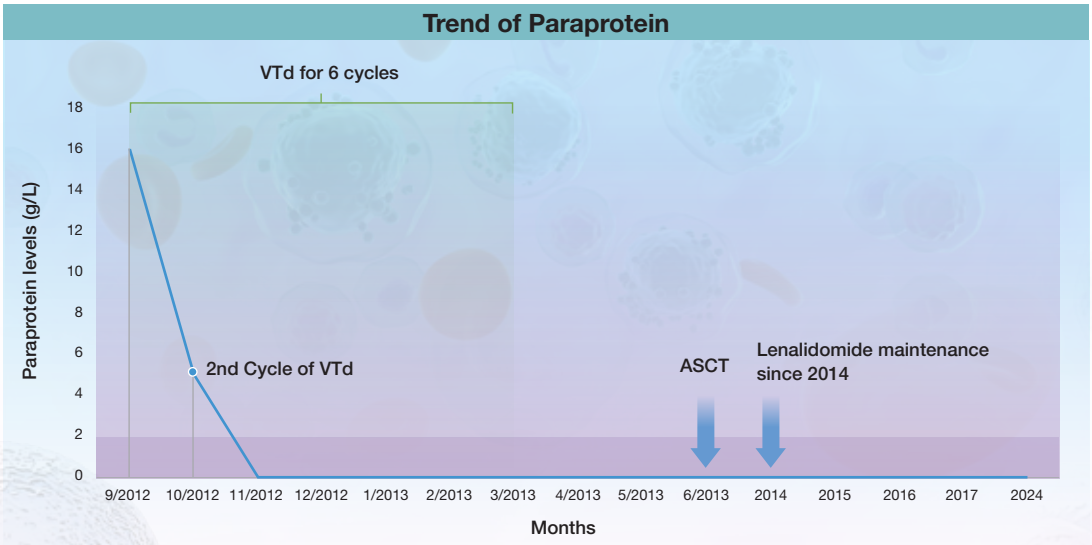

Figure 2. Trend of patient's paraprotein provided by Dr. Lau.

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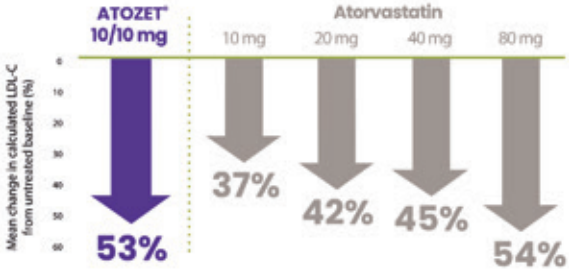

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Renal Function	Healthy	Stage 1	Stage 2	Moderate CKD Stage 3a	Moderate CKD Stage 3b	Severe CKD Stage 4	Severe CKD Stage 5
eGFR (mL/min/1.73m²)	Normal	90	60	45	30	15	
Atorvastatin	Atozet® (ezetimibe and atorvastatin) tablets	No dosage adjustment required					
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LDL-C: Low-density Lipoprotein Cholesterol; TC: Total Cholesterol, BP: Blood Pressure, CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; SCORE: Systematic Coronary Risk Estimation; OD: Once Daily.

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Reference: 1. Ballantyne, C.M. et al. Effect of Ezetimibe Coadministered With Atorvastatin in 628 Patients With Primary Hypercholesterolaemia - A Prospective, Randomized, Double-Blind Trial. Circulation.107,2409-2415 (2003). 2. Cooney, M.T., Bruckert E., Cordero A., Corsini A., Giannuzzi P. (2018). 2018 ESC/EAS guidalines for the management of dyslipidaemias. Eur Heart J, 37, 2999- 3058. 3. ATOZET Malaysia Prescribing information. LPC-MKOR53C-T-122018

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by Dr. Roy Lau

Optimising Protein Intake in Patients with Chronic Kidney Disease

Dr. Terry Ting Ho-yan

Registered Dietitian (UK)
Honorary Member, Hong Kong Nutrition Association

Chronic kidney disease (CKD) is a global public health problem that an estimated 843.6 million individuals are currently affected by various stages of the disease, whereas the prevalence of CKD is increasing, and Hong Kong is no exception[1]. Yet, the public awareness of CKD in Hong Kong, including the risk factors and dietary requirements of patients with the disease, is suboptimal. While protein restriction has long been used among CKD patients to delay the decline in kidney function, rigid dietary control is hard to follow in the long term and may increase the risks of malnutrition[2]. In this regard, supplementation with ketoanalogues (KA) coupled with a low-protein diet (KA-LPD) would reduce the risks of protein deficiency without increasing nitrogen burden and preserve kidney function in CKD patients. To uncover the dietary concerns in CKD and the clinical performance of KA, Dr. Terry Ting Ho-yan, a registered dietitian (UK), was invited to share his insights into optimising dietary management in CKD.

The Major Risk Factors of CKD

It has been reported that the most important risk factors for CKD include age, diabetes mellitus (DM), hypertension, and obesity[3]. Particularly, suboptimal controlled DM can lead to the development and progression of CKD that 29% to 38% of diabetic individuals develop CKD after a median follow-up of 15 years[4]. Besides DM, a local study by Wan *et al*. (2019) suggested that each 10 mmHg increase in systolic blood pressure (SBP) was associated with a 22% higher risk of CKD[5]. "It is very common that younger people who are not aware of their blood pressure develop CKD eventually," as per Dr. Ting. Similarly, a previous study reported that each rise in 1 unit of body-mass index (BMI) confers a 20% increase in the risk of CKD over 20 years[6]. Thus, proper control of glycaemic levels, blood pressure, and weight is paramount in reducing the risk of CKD.

Dr. Ting addressed that lifestyle factors, such as tobacco smoking and alcohol consumption, also increase the risk of CKD. Remarkably, he added that, while certain diseases and injuries would result in kidney impairment, improper use of medications, including Chinese herbal medicine and non-steroidal anti-inflammatory drugs (NSAIDs), can also lead to CKD. "Consulting healthcare professionals before taking medications is very important to prevent treatment-related adverse events," Dr. Ting advised.

The Progressive Damage to Kidneys

"Stage 1 to 3 CKD is usually asymptomatic and is not easy for patients to realise the disease unless regular blood tests are conducted," Dr. Ting noted. CKD is defined as an abnormality in kidney structure or function persisting for over 3 months. According to the KDIGO classification, CKD is classified based on the estimated glomerular filtration rate (eGFR), albuminuria, and cause of CKD. Briefly, stage 1 (eGFR of >90 ml/min/1.73m^2) represents a normal kidney function, whereas stage 2 (eGFR of 60-89 ml/min/1.73m^2) indicates a mild decrease in kidney function. When eGFR drops to 45-59 ml/min/1.73m^2 (stage 3a), mild-to-moderate decline in kidney function is indicated[7]. Dr. Ting outlined that increased serum level of creatinine becomes notable in stage 3a, whereas complications, such as imbalance of electrolytes and oedema, may be observed if eGFR further reduces to 30-44 ml/min/1.73m^2 (stage 3b)[7]. "At this stage (stage 3b), dietary restriction is needed to control blood glucose and pressure," Dr. Ting addressed.

Notably, an eGFR of 15-29 ml/min/1.73m^2 is classified as stage IV CKD, at which the kidney function is severely decreased with significant complications requiring more stringent symptom control measures. Eventually, an eGFR <15 ml/min/1.73m^2 indicated end-stage renal disease (ESRD), and renal replacement therapy is needed. A summary of KDIGO CKD definition and prognosis is illustrated in **Figure 1**[7].

Controlling Protein Intake – Protein Quality Matters

Given that protein restriction helps reduce the disturbances characteristic of uraemia and diminishes the ill effects of hyperphosphatemia, metabolic acidosis, hyperkalaemia, and

GFR categories, description, and range (mL/min/1.73 m^2)				Persistent albuminuria categories, description, and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30-300 mg/g	>300 mg/g
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Figure 1. *KDIGO Definition and prognosis of CKD by GFR and albuminuria categories, green: low risk; Yellow: moderately increased risk; orange: high risk; red: very high risk*[7]

other electrolyte disorders, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines advocate considering a LPD for patients with CKD. For instance, a controlled LPD providing 0.55-0.60 g protein/kg body weight/day or a very low-protein diet (VLPD) providing 0.28–0.43 g protein/kg body weight/day with additional keto acid/amino acid analogues is recommended for CKD patients who are not on dialysis and without diabetes[8].

Regarding protein intake, Dr. Ting emphasised that, apart from common protein-rich food, such as eggs, meat, fish, milk, and bean products, there are low-quality proteins in carbohydrate-rich food, such as wheat gluten. Protein quality refers to the availability of amino acids that it supplies[9]. Hence, it is crucial to consider the low-quality protein contents in designing recipes for LPD. "Even though the meat consumption is low, a large amount of rice intake will increase the total protein intake," Dr. Ting noted. The protein quality represented by the Protein Digestibility Corrected Amino Acid Score (PDCAAS) of some food substances is shown in **Figure 2**[9].

Implementing LPD involves significant changes in dietary habits, which may be difficult practically. Thus, Dr. Ting suggested that a stepwise approach can be considered. Furthermore, he highlighted that referral to dietitians for advice on dietary planning is desirable for CKD patients with stage 3 disease or above.

The Roles of KAs in Optimising LPD

If the protein intake is well-restricted, KAs of essential amino acids (EAAs) can utilise circulating amino groups to transfer themselves into EAAs through the transamination effect. Hence, supplementation with KAs can reduce the risks of protein deficiency without increasing the nitrogen burden for patients on LPD or VLPD[2].

While clinical guidelines recommend supplementation with KAs for CKD patients[8], Dr. Ting stated that KA-LPD has long been used in local clinical practice. "KAs allow the reduction of

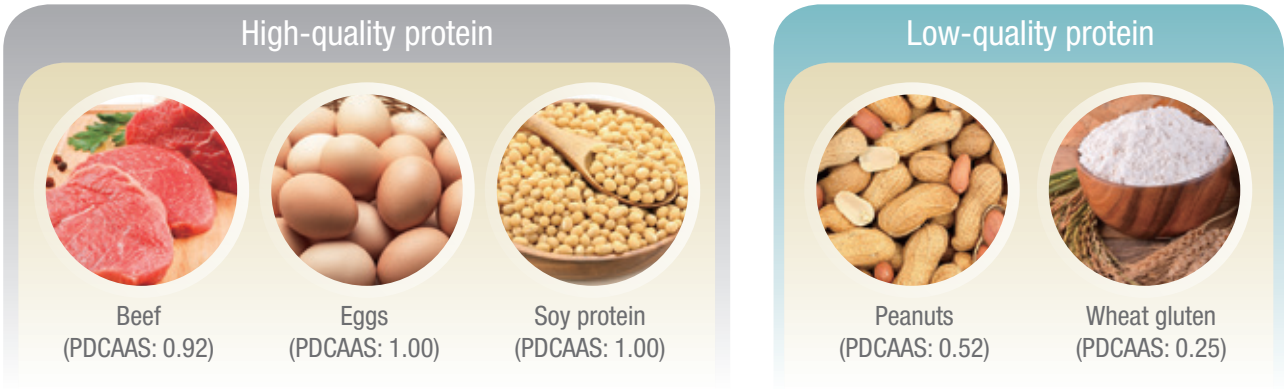

Figure 2. Protein quality of common food products[9], PDCAAS: Protein Digestibility Corrected Amino Acid Score

dietary protein intake to an average of about 0.6 or even 0.5 g protein/kg body weight/day. While reducing the workload of the kidneys, KAs slow down the progression of kidney impairment and the effect of uraemia," Dr. Ting said. He added that, based on his clinical observation, no clinically significant adverse events are associated with the use of KAs. However, he reminded that consulting healthcare professionals before using KAs is essential for achieving optimal outcomes.

The Clinical Benefits of KAs

The clinical benefits of KA-LPD have been demonstrated in various clinical trials. The retrospective cohort study involving 1,042 pre-dialysis CKD patients (stage 3-5) received KA-LPD by Ariyanopparut *et al*. (2022) revealed that, after a median follow-up of 32.9 months, patients received KA-LPD had a significantly lower risk of kidney function decline (hazard ratio [HR]: 0.13, p <0.001) and dialysis initiation (HR: 0.24, p <0.001, **Figure 3**) than those received LPD alone after adjusting for confounders[10].

On the other hand, a retrospective analysis including 541 patients with stage 4 CKD received KA-LPD by Yen *et al*. (2022) demonstrated that continuation of KA-LPD (n=303) exhibited a significantly lower incidence of new-onset ESRD requiring maintenance dialysis (6.8% vs. 10.4%, HR: 0.62, p =0.023) than those discontinued supplementation with KAs (n=238, **Figure 4**)[2]. Based on the clinical studies above, initiating KA-LPD and continuing the KA supplementation would reduce the short-term risk of commencing dialysis.

Apart from pre-dialysis CKD patients, Dr. Ting noted that KA supplementation can be prescribed for ESRD patients to preserve their residual kidney functions. "In patients receiving dialysis treatment, KA supplementation helps maintain the patient's residual kidney function and, hence, increases the efficacy of dialysis," he highlighted. Moreover, while KA supplementation is prescribed for patients with stage 5 CKD, there are studies investigating the clinical outcomes of early use of KA-LPD[11].

Getting the Right Advice from the Right Sources

Based on the published clinical data, KA-LPD is effective in preserving kidney functions for CKD patients, with no clinically significant adverse events observed. Nonetheless, Dr. Ting addressed that many CKD patients adopted a too stringent dietary control, which potentially leads to suboptimal outcomes. "Although control of dietary potassium and phosphorus intake is important, the level of control varies according to the stage of the disease, but not the lower, the better," he stated. Besides, he pointed out that patients are nowadays flooded with dietary information from the internet, whereas a substantial proportion of them may not be accurate. In particular, there are opinions advocating the keto diet and low-carbon diet, which may not be suitable for CKD patients.

As a final remark, Dr. Ting stressed that consulting nephrologists and dietitians is essential in planning the diet for CKD patients. In particular, while many CKD patients concern about the impact of protein restriction on their daily food options, dietitians play a key role in designing suitable recipes for them, balancing the low-protein requirements and patient's enjoyment of food.

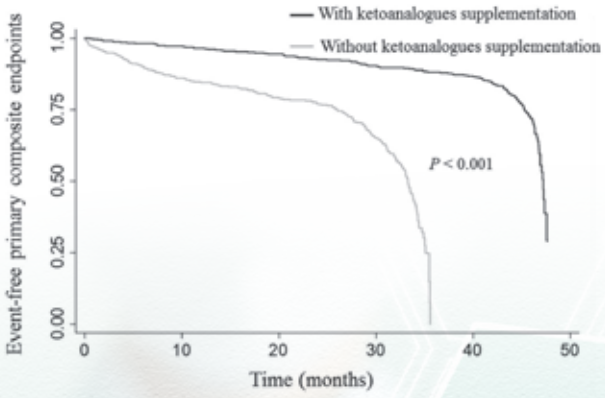

Figure 3. Kaplan-Meier estimates of primary composite endpoint[10], defined as an annual eGFR decline of more than 5 ml/min/1.73 m2 or long-term dialysis initiation

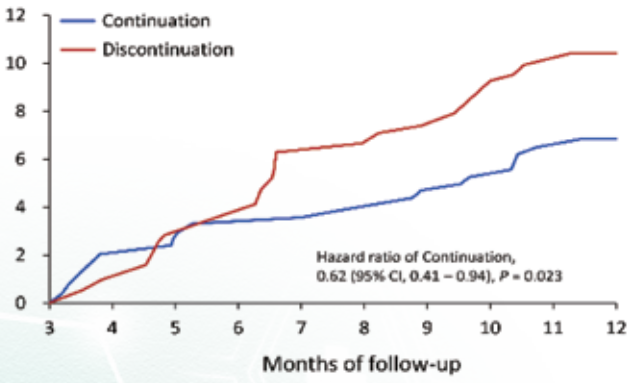

Figure 4. Cumulative event rate of ESRD requiring dialysis[2]

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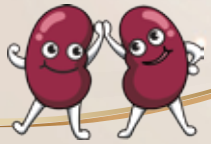

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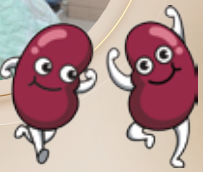

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Hepatocellular Carcinoma: A Disease with Ethnic & Geographic Differences

Hepatocellular carcinoma (HCC) is ranked as the sixth most common cancer worldwide and its incidence has been progressively increasing. HCC is also the third most common cause of cancer-related death, with a 5-year survival rate of just 3%[1]. Interestingly, HCC incidence and outcomes vary significantly across different ethnic groups. In the United States, non-White populations, including Asian Americans, Pacific Islanders, American Indians, Alaska Natives, Hispanics, and African Americans, have a higher risk of developing HCC compared to White populations . Furthermore, minority populations often face unique challenges that contribute to disparities in HCC outcomes[2]. Geographical differences also exist. More than half of the world's estimated cases from liver cancer occurred in Eastern Asia (54.3%) in 2020, and China alone was home to 45.3% of the world's liver cancer cases (Figure 1)[3]. In China, delayed diagnosis is common, leading to a worsened prognosis[4]. In view of this phenomenon, this article delves into the underlying causes of these disparities, as well as providing a brief description of treatment options and preventive measures. The mechanisms behind the ethnic and geographic differences in HCC are multifaceted, influenced by a combination of genetic, environmental, and socioeconomic factors.

Genetic Factors

Ethnic and geographical disparities in the incidence of HCC are associated with certain genetic factors[5]. Certain driver genes, such as *TP53* and *CDKN2A*, may contribute to increased susceptibility to HCC in Asians compared to whites. Therapeutically targeting these genes might prevent HCC disparities. Also, higher expression of SATB2 may be responsible for the disparity in HCC outcomes[6].

Hepatitis B Virus (HBV) Infection

HBV infection is the main cause of HCC. Worldwide, it is estimated that 44% of the HCC cases are attributed to chronic HBV infection; and the majority of such cases occur specifically in East Asia. Chronic HBV infection may be associated with a 5 to 100 fold increase in the risk of developing HCC[6]. In China, there are approximately 30 million people chronically infected with HBV, accounting for nearly one-third of the world's HBV infection[7].

Hepatitis C Virus (HCV) Infection

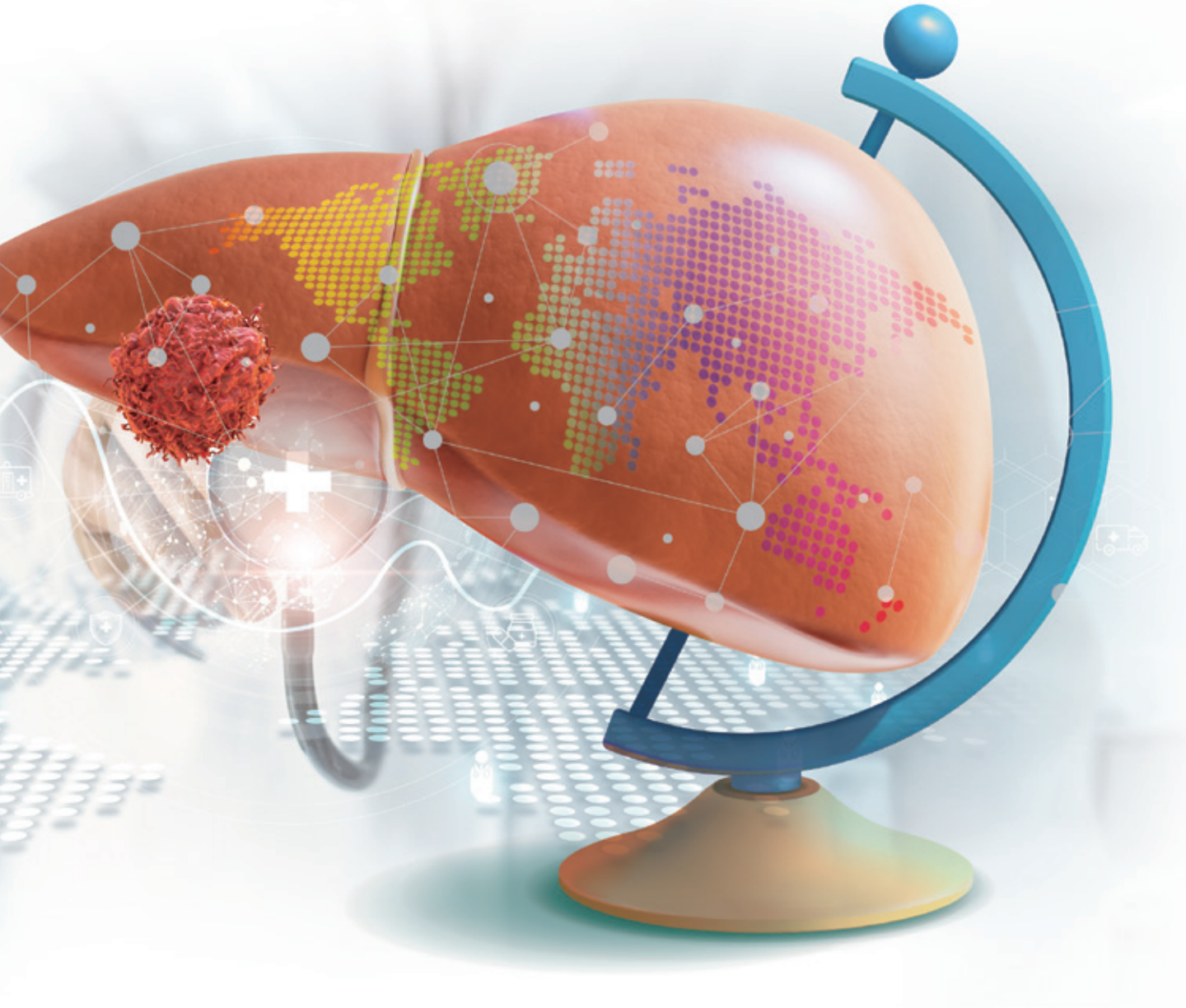
An estimated 50–60% of HCC patients suffer from HCV infection in the United States; and in contrast to HBV, chronic HCV infection can cause a 15 to 20 fold increase in the risk for HCC. HCV infection is highly prevalent and causes high mortality in the African American population compared to the Caucasians or other ethnic groups[6].

Aflatoxin Exposure

Aflatoxins are toxins produced predominantly by two fungi: *Aspergillus flavus* and *Aspergillus parasiticus*. Contaminated animal and plant products are the major sources of aflatoxins. There are four aflatoxins (B1, B2, G1, and G2) that have been shown to act as a carcinogen in both humans and animals. Aflatoxin B1 (AFB1) is the most potent liver carcinogen[6]. In China, the aflatoxin contamination rates in corn and peanuts reached as high as 70.27% and 24.24%, respectively. High aflatoxin exposure in certain areas of China may account for its high HCC prevalence[7].

Lifestyle Factors

Alcohol use, either as a primary factor or in combination with HBV, HCV or diabetes, can result in the development of HCC. According to a survey, the highest rate of heavy drinking (31.6%) was observed in Hispanics compared to other ethnic minorities[6]. It is reported that the average alcohol consumption among the Chinese population (7.2 L of pure alcohol) was 12.5% higher than the global average (6.4 L)[7]. Smoking is thought to be another risk factor for HCC[7]. Ironically, China is



the largest producer and consumer of tobacco in the world. There are more than 300 million smokers in China, nearly one-third of the world's total. More than half of adult men are current tobacco smokers. About one in every three cigarettes smoked in the world is smoked in China[8].

Socioeconomic Factors

In the United States, HCC disproportionately affects disadvantaged populations, with the highest age specific rates among ethnic minorities[6]. Disparities in healthcare access, health literacy, and socioeconomic status may play a crucial role. Minority populations often face barriers to early detection and treatment, which can lead to poorer outcomes[2]. In China, the mortality rates of liver cancer vary significantly among eastern, central, and western parts of the country, consistent with the uneven economic development across different regions in China[7].

Treatment Options

Treatment for HCC depends on the stage of the disease and the overall health of the patient. Surgical resection or liver transplantation can be curative for early-stage HCC. According to a recent meta-analysis, liver transplantation was associated with significantly better 5-year overall survival (OS) (64.83%) and recurrence-free survival (RFS) (70.20%) than liver resection (OS: 50.83%, odds ratio [OR]: 1.79, P < 0.001; RFS: 34.46%, OR: 5.32, P < 0.001)[9]. Techniques such as radiofrequency ablation (RFA) or cryoablation can be used to destroy cancer cells in localized tumors. Cryoablation has been found to be non inferior to RFA therapy for single HCC patients without lymph node invasion or distant metastasis[10]. Important progress has been made in the treatment of advanced HCC during the last two decades, by using targeted therapy agents which target specific pathways involved in cancer growth. Immunotherapy, including checkpoint inhibitors, has also shown promise in treating advanced HCC[11]. Additionally, radiation therapy can be used to control symptoms and slow the progression of the disease in advanced stages[12].

Prevention Tips

The prevention of HCC involves addressing its primary risk factors. First of all, hepatitis B vaccination is a critical preventive measure, especially in regions with high HBV

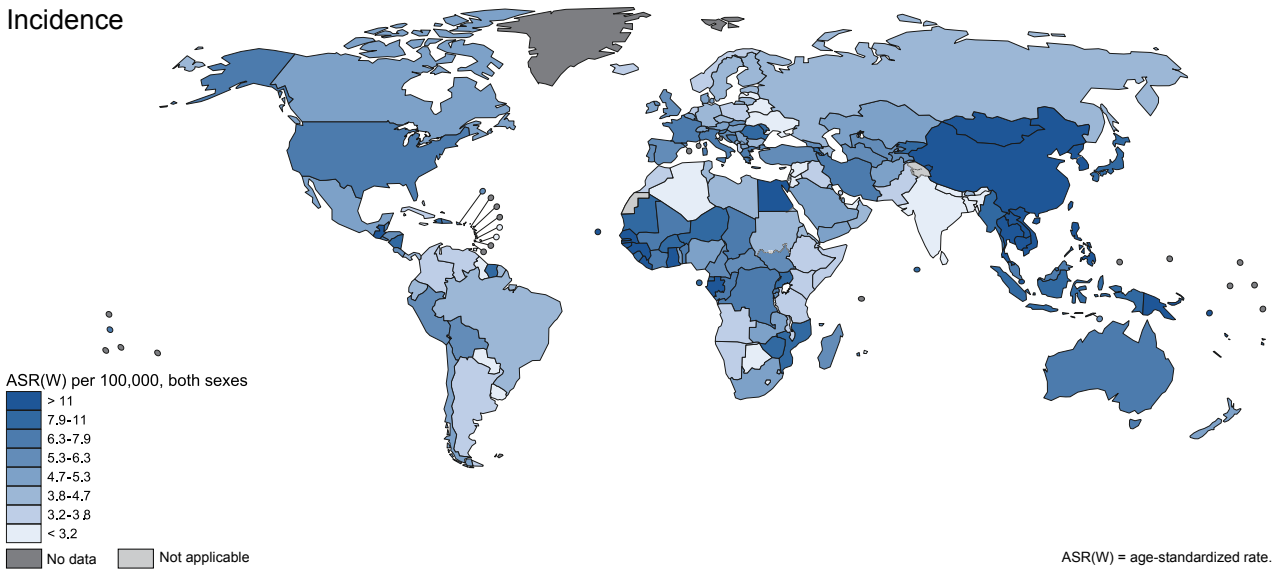


Figure 1. Age-standardized liver cancer incidence rate per 100,000 people in 2020, by country[3]

prevalence, such as China. Neonatal hepatitis B vaccination has proven effective in China in preventing HBV-related HCC[13,14]. Secondly, patients with chronic hepatitis B infection are recommended to routinely undergo screening for HCC, as HCC screening can be associated with a substantial reduction in HCC-related mortality in such patients[15]. Thirdly, lifestyle modification is also crucial — Reducing alcohol consumption, maintaining a healthy weight, and managing conditions like diabetes and nonalcoholic fatty liver disease can lower the risk of HCC[13]. Additionally, it is worthy of note that exposure to aflatoxins is associated with an increased risk of HCC. Aflatoxins are a family of toxins produced by certain fungi that are found on agricultural crops such as maize and peanuts. Therefore, minimizing exposure to aflatoxins can reduce the risk of HCC, particularly in developing countries[16].

Finally, addressing HCC disparities requires a patient-centered approach that incorporates infrastructure enhancements, policy changes, and improved access to care[2].

Conclusion

Hepatocellular carcinoma is a complex disease with significant ethnic and geographical disparities in incidence and outcomes. Understanding the mechanisms behind these differences and implementing effective treatment and prevention strategies are crucial in reducing the global burden of HCC. Collaborative efforts among healthcare providers, researchers, and policymakers are essential to ensure equitable care for all individuals affected by this challenging disease.

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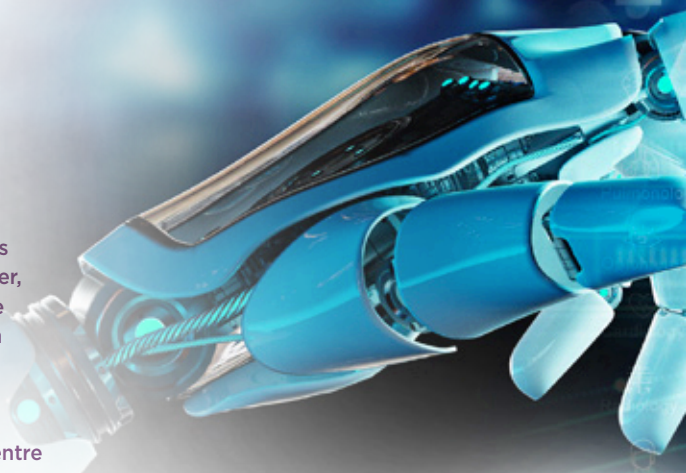
by Dr. Mohsin Roshan

Unravelling the Complexity of Prostate Cancer

Professor Ng, Chi Fai, Anthony

Director and Professor of S.H. Urology Centre,
Department of Surgery,
The Chinese University of Hong Kong (CUHK)



Prostate cancer (PCa) is a complex disease that affects millions of males, globally. It is the 3rd most common cancer in males and the 4th leading cause of male cancer-related deaths in Hong Kong[1]. The aetiology of PCa is believed to be related to several risk factors which includes the male gender, old age (aged ≥50 years), positive family, obesity, diet and ethnicity[2]. More important, PCa often follows an indolent clinical course since patients with PCa often remain asymptomatic during the early stages of the disease[3], thus, at diagnosis, the disease is often at late stages, requiring extensive treatment[4]. Therefore, to understand the complex nature of PCa, we have invited Professor Ng Chi Fai, a specialist, and director of SH Ho Urology Centre at the Chinese University of Hong Kong (CUHK) to discuss the reasons behind the late diagnosis of the disease, in addition to provide an overview on the treatment in early and advanced stages of the disease, particularly the use of robot-assisted radical prostatectomy (RARP), and the integration of artificial intelligence (AI) into clinical practice.

Unveiling the Hidden Danger of Prostate Cancer

Prostate is an accessory reproductive organ in males, primarily responsible to complement the essential secretions to semen, and to keep the sperm viable. Notably, the adult prostate is divided into central, transitional and peripheral regions, with 95% of PCa cases occurring at the peripheral zone of the prostate[5] with an acinar origin[6]. More importantly, PCa is common in male, accounting for 1 in every 14 cancers diagnosed globally, and 15% of all cancers reported in males[7]. Locally, PCa is the 3rd commonest cancer in males and the 4th leading cause of male cancer-related deaths1. Naturally, PCa is associated with a number of risk factors as Prof. Ng explained that these risk factors include the male gender, old age (males ≥ the age of 50), positive family history, obesity, diet (westernised diet), and ethnicity (higher prevalence in Blacks and Caucasians)[2]. Here, Prof. Ng added that male with a first-degree relative (father or brother) with PCa have twice the risk of developing PCa compared to the general population[2].

Fortunately, most localised PCa run a relative indolent course, with population studies indicating it as slow progression disease with limited aggressiveness[3]. Nevertheless, patients with early PCa often remain asymptomatic, and up to 14% of patients with PCa demonstrate metastatic disease at the time of diagnosis[4]. Why? Prof. Ng highlighted that even though early diagnosis of PCa remains the cornerstone, most patients with early PCa may not recognise symptoms until they are well into the late stages of the disease, requiring aggressive treatment. In fact, up to 75% of patients with PCa experiences metastatic bone disease which often leads to an increased risk for skeletal-related events (SREs), including pathological bone fractures, spinal cord compression, and hypercalcaemia[8]. More worryingly, recent population-based studies have reported that 86% of the patients associated PCa with symptoms, but

only 1% were aware that it could be asymptomatic[5]. Prof. Ng stressed a salient point that males with early staged disease often hesitate to seek help early compared to female, and they only seek help when the disease is in advanced stages[9].

An Era of Precision Oncology

The standard diagnostic tools for detecting PCa include a digital rectal examination (DRE), followed by a blood-based analysis of prostate specific antigen (PSA) and imaging. What is DRE and how does it help with the diagnosis? DRE is a physical palpation of the prostate to assess the gland enlargement, texture and stiffness with a positive predictive value in detecting PCa of 5-30% in males with PSA levels of ≤2 ng/ml[10]. A prostate biopsy (needle biopsy) is indicated for an abnormal DRE result, which is associated with a worse differentiation grade, but considered as a definitive diagnosis. What about the serum PSA? Serum PSA may complement prostate cancer detection efforts, but like DRE, PSA testing can be abnormal without PCa being present (false-positive) and can be normal, though rare, despite the presence of PCa (false-negative)[10]. Prof. Ng reminded us that PSA is a very sensitive but relatively non-specific and imprecise screening tool, as both benign and malignant processes will cause an elevation in serum PSA levels[4]. Hence, multiple factors should be considered in patients with a rise in serum PSA. Factors that influence the survival of PCa patients are dependent on the clinical stage of the tumour, the histological grade of tumour, patient's comorbid-adjusted life expectancy, and the PSA level[11].

After the initial diagnosis, the disease is usually staged (stage I-IV) and treatment depends on the tumour's stage and grade. For instance, radical prostatectomy or external beam radiation therapy is considered for patients with intermediate to high-risk localized PCa. Contrary to this, brachytherapy or focal therapy, such as cryotherapy, are treatment options for

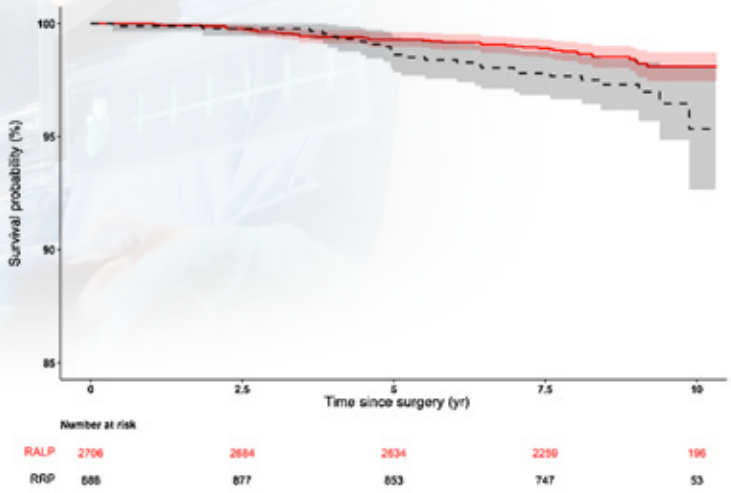


Figure 1. *Prostate cancer-specific mortality for RALP versus RRP and for D'Amico[20]. Stratification by D'Amico risk groups (low, intermediate, and high risk). RALP = robot-assisted laparoscopic prostatectomy; RRP = open retropubic radical prostatectomy.*

patients with more focal disease and low to intermediate-risk diseases [12], according to Prof. Ng. He elaborated further that patients, due to the slow-growing nature of PCa, patients, particularly the elderly, with low-risk to very low-risk diseases may consider active surveillance[13]. What about the treatment options for advanced PCa? It has long been known that PCa is unique since it is highly dependent on androgen for growth and progression; therefore, androgen deprivation is an effective therapeutic strategy widely used in clinical practice[14]. Prof. Ng explained further that androgen deprivation therapy (ADT) often induced PCa regression and prolonged survival for these patients[15]. However, he warned like other hormone-replacement therapies (HRTs), patients may experience adverse events associated with the ADT, which include increased cardiometabolic risk, hot flushes, loss of libido, erectile dysfunction, depression, anaemia, and osteoporosis[16]; fortunately, these are manageable adverse events.

The Golden Age of Robotic Surgery in Prostate Cancer Management

Radical prostatectomy is the recommended surgical treatment for clinical localised PCa, which provides long-term oncological control. Traditionally, open retropubic radical prostatectomy (RRP) had often been utilised, but due to the complexity of the pelvic anatomy, particularly, because the prostate lies deep and is often hard-to-reach[17]. Thus, a minimally invasive method such as laparoscopic prostatectomy was initially developed but failed to take off as a mainstream treatment due to the technical difficulties associated with the technique[17]. The shortfalls related to the laparoscopic prostatectomy were overcome by robot-assisted surgery that has since transformed the landscape of urological interventions. One such advance includes the use of RARP for the management of PCa. The procedure was introduced in 2002 by Binder and marked a significant milestone by combining the advantage of minimally invasive radical prostatectomy with enhanced surgeon ergonomics and improved technical ease in vesicourethral anastomosis reconstruction[18]. Prof. Ng explained that RARP has generally been accepted to have a lower estimated blood loss and shorter hospital stays with lower intraoperative adverse event rates when compared to traditional radical open prostatectomy[19].

These findings have been substantiated in a prospective multicentre controlled trial, study by Lantz *et al*., 2021 that evaluated the functional and oncological long-term outcomes 8 years after robot-assisted laparoscopic prostatectomy (RALP) and open retropubic radical prostatectomy (RRP). The primary endpoint of the study was urinary incontinence, and the results showed that the incidence of urinary incontinence was not significantly different at 8 years after surgery between RALP and RRP (27% vs 29%). However, the incidence of erectile dysfunction was significantly lower in the RALP group (66% vs 70%; adjusted risk ratio [aRR] 0.93, 95% confidence interval [CI] 0.87-0.99)[20]. Furthermore, prostate cancer-specific mortality (PCSM) was significantly lower in the RALP group at 8 years after surgery (**Figure 1**). The conclusion reached here was that robot-assisted minimally invasive techniques are safe in the long-term[20]. Similarly, a systematic review and meta-analysis by Wang *et al*., 2023 on prospective studies comparing RARP with open radical prostatectomy concluded that RARP was superior to open radical prostatectomy in terms of hospital stay, blood loss, transfusion rate, complication, nerve sparing, postoperative erectile function recovery and biochemical recurrence[21].

Artificial Intelligence, a New Tool Against Prostate Cancer

AI application has enabled remarkable advancements in healthcare delivery and to improve accuracy, as well as the efficiency of diagnostic imaging interpretation[22]. Currently, there is a widespread potential of AI in the field of Urology, particularly in the diagnosis, and the treatment of PCa, Prof. Ng commented. He elaborated that many studies have shown that AI-powered systems can accurately detect PCa and help predict patient outcomes, leading to a higher potential to improve patient care[23], locally. To showcase the potential AI in clinical practice, Saha *et al*., 2024 performed an international, paired, non-inferiority, confirmatory study that compared the performance of AI systems at detecting clinically significant PCa on MRI in comparison with radiologists using the Prostate

Imaging-Reporting and Data System version 2.1 (PI-RADS 2.1) and the standard of care in multidisciplinary routine practice. Interestingly, among 10,207 examinations conducted from January 1st, 2012, through December 31st, 2021, 2,440 cases had histologically confirmed Gleason grade 2 or greater PCa. The results demonstrated that AI system was superior to radiologists using PI-RADS (2.1), on average, at detecting clinically significant PCa and comparable to the standard of care[24]. These findings demonstrated the potential of AI as a supportive tool within a primary diagnostic setting.

The role of AI in diagnosing PCa has recently been explored in a retrospective study by Hamm *et al*., 2023. The aim of this study was to develop an explainable AI (XAI) model for clinically significant PCa diagnosis at biparametric magnetic resonance imagining (MRI) using Prostate Imaging Reporting and Data System (PI-RADS) features for classification justification. Among 1,244 males (median age of 67 years) with 3,260 prostatic lesions (372 lesions with Gleason score of 6; 743 lesions with Gleason score of ≥ 7; 2,145 benign lesion), XAI reliably detected clinically significant PCa in internal and external test sets with a sensitivity of 93% and an average of one false-positive findings per patient. Furthermore, the XAI-assisted readings improved the confidence of non-experts in assessing PI-RADS 3 lesions, reducing the reading time by 58 seconds (p=0.009). These results demonstrated that AI integration in clinical practice can help reliably detect, and classify clinically significant PCa and improve the confidence and reading time of non-expert in the field of urology[25]. Here, Prof. Ng added that AI integration has already been implemented at the CUHK as a trial, and hopefully, this will invariably support clinicians in many different specialities. He also reminded us that PCa is becoming more common locally with an ageing population. Thus, it is crucial for clinicians to use different diagnostic modalities to identify the disease and treat it as early as possible to reduce the disease burden.

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by Dr. Mohsin Roshan

Ushering a New Era for Rabies Prevention

Rabies is a zoonotic, and progressive neurological infection caused by Lyssavirus, affecting both animals and humans. Notably, more than 99% of human rabies are transmitted by unvaccinated dogs, and the disease affects more than 100 countries globally. Currently, there are rabies immune globulins (RIG) that are used as post-exposure prophylaxis (PEP) for individuals exposed to rabies. However, due to limit availability and safety concerns of RIGs (human RIG and equine RIG), a newer treatment approach utilising a mixture of two humanised monoclonal antibodies (mAbs) to provide a better coverage against different strains of rabies virus (RABV) has been considered. The aim of this article is to review the disease burden related to rabies, in addition to discuss the upcoming potential treatment which may help change the landscape of rabies and help countries achieve the "Zero by 30" target set by the World Health Organisation (WHO).

Rabies, a Silent Killer on the Loose

Rabies is a zoonotic, and progressive neurological infection caused by Lyssavirus, typically affecting all and warm-blooded animals[1]. Remarkably, once clinical symptoms appear, rabies carries a 100% fatality rate[2]. Notably, more than 99% of human rabies case are transmitted via unvaccinated dogs[2], affecting more than 100 countries globally, and rabies is slowly becoming the leading cause of death related to zoonotic aeitology[3]. Strikingly, rabies causes approximately 59,000 deaths and loss of more than 3.7 million disability adjusted life years (DALYs) annually, with most reported cases originating in rural areas of Africa and Asia[3]. One of the major contributing factors to this significant burden is the low availability of safe, affordable and effective biologics[4]. According to the WHO, early administration of immune globulins and vaccine remains an important aspect for the prevention of rabies by PEP (**Figure 1**)[5].

Currently, PEP used against rabies include RIGs which are either prepared from humans (HRIG) or equine (ERIG) plasma. However, concerns are raised regarding their safety, immunogenicity, sustainability, and batch-to-batch variations, which had led to the pursual of a replacement to RIG[4]. Very recently, the WHO has recommended combining mAbs that target at least two non-overlapping epitopes on the RABV glycoprotein to overcome current RIG limitation, as well as maintaining the breadth of cross-reactivity necessary for effective protection[4]. This has ushered a new treatment era with the introduction of SYN023*, which is a mixture of two humanised monoclonal IgG kappa antibodies, CTB011 and CTB012, that bind to non-overlapping epitopes within highly conserved regions of the RABV outer enveloped glycoprotein[6].

Unleashing the Power of Monoclonal Antibodies

The humanised mAbs are an ideal alternative to RIG since they are more affordable, accessible, and standardised[7]. Even though there are currently five mAbs that has been tested in clinical trials, not all mAbs have equal neutralising power. For instance, the first mAb was approved by the Indian Regulatory Agency in 2016 against RABV, however, it has shown to be ineffective in neutralising a rare rabies variant found in the Peruvian Bats[8]. Why? It may be due to the fact that the formulation only contains one type of mAb[7], therefore, deemed ineffective against other strains of the virus. On contrary, the SYN023*, a mixture of two anti-rabies humanised IgG1 kappa mAbs may help overcome the shortfalls of other ineffective mAbs currently available in the market since SYN023* is able

Categories of contact with suspect rabid animal	Post-exposure prophylaxis measures
Category I • Touching or feeding animals, animal licks on intact skin (no exposure)	Washing of exposed skin surfaces, no PEP
Category II • Nibbling of uncovered skin • Minor scratches or • Abrasions without bleeding (exposure)	Wound washing and immediate vaccination
Category III • Single or multiple transdermal bites or scratches • Contamination of mucous membrane or broken skin with saliva from animal licks • Exposures due to direct contact with bats (severe exposure)	• Wound washing • Immediate vaccination • Administration of rabies immunoglobulin/ monoclonal antibodies

Figure 1. Category II and III exposures require human rabies vaccination[5]

to neutralise more than 15 contemporary clinically isolated stains of rabies collected from China and 10 predominant strains in the United States (US)[7]. The effectiveness of SYN023* was evaluated in a phase 2b randomised controlled trial (RCT) by Quiambao *et al*., (2024). 448 patients in two risk substrata of WHO Category III exposure were randomised to receive either 0.3 mg/kg SYN023* or 0.133 mL/kg HRIG injected in and around the wound site(s) plus a course of rabies vaccination. Patients were followed for safety and absence of rabies for ≥1 year.

Remarkably, the geometric mean titer (GMT) for serum rabies virus neutralising activity (RVNA) was higher with the SYN023* throughout 2-weeks post-treatment period. Strikingly, 99.4%

of SYN023* recipients had proactive RVNA levels on Day 4 compared to only 4.5% of HRIG recipients. These differences widened even further on the day 8 with 98.1% of SYN023* recipients were protected against RABV compared to only 12.2% of HRIG recipients. These findings support the notion that the anti-rabies immune response with SYN023* was non-inferior to HRIG since the SYN023*: HRIG ratio of RVNA GMTs at day 8 was 19.42, exceeding the 10% superiority margin (p<0.0001) (**Figure 2**)[6]. Here, SYN023* demonstrated its ability to provide a higher RVNA than HRIG soon after rabies exposure, especially at WHO Category III exposure[6]. In the wake of rising rabies cases globally, especially after the coronavirus-2019 (COVID-19) pandemic, the four world bodies, namely the WHO, the Food and Agriculture Organisation (FAO), the World Organisation for Animal Health (OIE), and the Global Alliance for Rabies Control (GARC) endorsed forming a global support system to eradicate the disease by the year 2030 (Zero by 30)[9]. This framework calls for extending the vaccination of dogs to reduce the risk of human rabies, in addition to curb the global rising rabies cases with a better disease management[9]. In conclusion, rabies is a deadly infectious disease that targets different organs, particularly the brain and the lungs[10]. Considering dog bites being the main source of transmission of this disease, appropriate administration of anti-rabies vaccines and immune globulins remains vital for rabies prevention and eventual eradication.

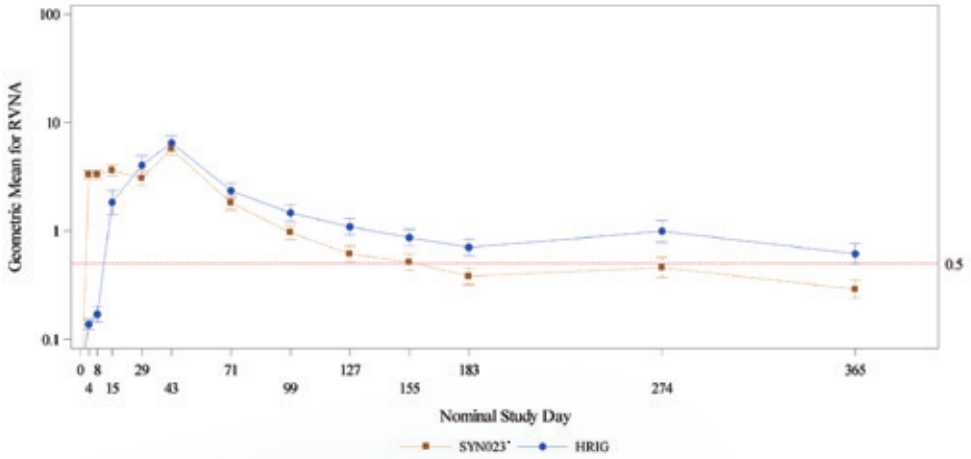

Figure 2. Geometric Mean Rabies Virus Neutralising Activity over the study period- Normal risk group per protocol population error bars denotes 95% confidence interval. Rabies virus neutralising activity (RVNA) values less than the assay lower limit of quantitation (LLoQ) were set to LLoQ/2 (0.05 IU/mL) for geometric mean RVNA calculation[6]. HRIG= human-derived rabies immunoglobulin, RVNA= rabies virus neutralising activity.

Footnote

*SYN023 is currently not approved by the European Medical Agency (EMA) and Food and Drug Administration (FDA). It is only approved for clinical trials by the Chinese Food and Drug Administration (CFDA) in June 2017[7].

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by Dr. Mohsin Roshan

Is the Era for Trabeculectomy Over for Advanced Glaucoma?

A Journey Through Glaucoma

Glaucoma is a collection of diseases which inadvertently causes an increase in the intraocular pressure (IOP), thereby, affecting the optic nerve and the visual fields. It affects about 70 million individuals and is the second leading cause of blindness globally. Notably, the risk factors for glaucoma includes having refractive error, chronic topical or systemic corticosteroid use, head or ocular trauma, previous ocular history and family history of glaucoma. Clinically, glaucoma can be divided into open-angle and closed-angle glaucoma, both of which can have primary or secondary causes[1]. Not surprisingly, 80% of all cases of glaucoma are open-angle glaucoma (OAG), a chronic, progressive, and irreversible multifactorial optic neuropathy that is characterised by optic nerve head changes, retinal nerve fibres layer thinning, and progressive loss of peripheral vision[1]. Primary OAG (POAG) is the commonest subtype, characterised by increased resistance to drainage in the trabecular meshwork.

However, the drainage angle between the cornea and iris remains open, but due to the blockage, the intraocular pressure (IOP) gradually rises causing optic nerve damage and progressive visual loss[1]. Considering glaucoma is typically an asymptomatic disease in its early stages, it is not uncommon for late diagnosis to occur with advanced glaucomatous damage already present[2]. Interestingly, the guidelines from the National Institute for Health and Care Excellence (NICE) suggested that patients presenting with advanced disease should be offered trabeculectomy as a primary intervention over the medical treatment; however, due to lack of evidence supporting primary surgery in such cases, most patients with advanced glaucoma often receive medical management initially, followed by trabeculectomy if medical management remains unsuccessful[3]. Nevertheless, some argued the validity for such approach since recent studies have suggested patients with advanced glaucoma may benefit from early surgical management to optimise their treatment outcome, in addition to improve their quality of life (QoL)[4].

A Surgical Approach to Advanced Glaucoma

Visual impairment resulting from glaucoma is often preventable if it is diagnosed and treated early. However, since most patients with glaucoma remains asymptomatic during the early phase of the disease, they often present with symptoms when the disease is in more advanced stages. In fact, around 25% of patients with glaucoma demonstrate advanced disease in at least 1 eye at presentation in the United Kingdom (U.K.) and reducing IOP remains the only proven effective treatment against glaucoma with raised IOP[4]. Currently, there are two treatment options for patients with an advanced disease and they include the medical management

and surgery. Remarkably, a Cochrane systematic review comparing primary medical versus surgical treatment for OAG based on 4 trials involving 888 patients with previously untreated OAG concluded that trabeculectomy may lower the IOP more than the medical treatment in patients with glaucoma; however, the trial excluded patients with more advanced disease, thus, these findings may not be applicable for patients with more advanced disease[5]. However, a 5-year multicentre randomised controlled trial by King *et al*., (2024) evaluated the effectiveness of primary trabeculectomy against medical treatment in patients with advanced glaucoma.

453 adults with newly diagnosed advanced OAG in at least 1 eye were recruited from 27 secondary care glaucoma departments in the U.K., 227 were allocated to trabeculectomy

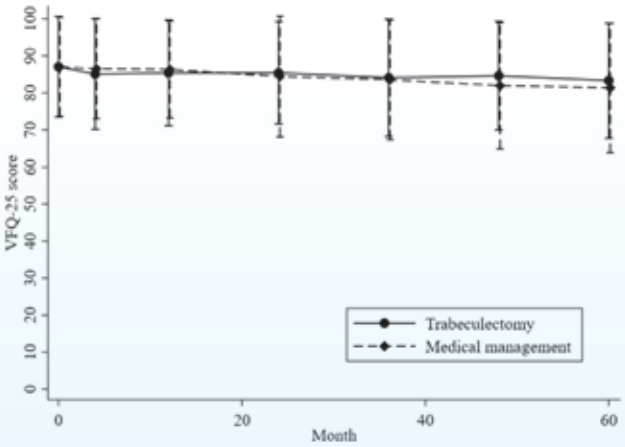


Figure 1. *Quality-of-life outcomes up to 5 years for the 25-item Visual Function Questionnaire (VFQ-25)[4].*

and 226 were allocated to the medical management. The primary outcome was vision-specific QoL measured with the 25-item Visual Function Questionnaire (VFQ-25) at 5 years and secondary outcomes were general health status, glaucoma-related QoL, clinical effectiveness (IOP, visual field, and visual acuity), and safety. Remarkably, at 5 years, the VFQ-25 scores for trabeculectomy and medication arms were 83.3 ± 15.5 and 81.3 ± 17.5, respectively (**Figure 1**). The mean IOPs were 12.07 ± 5.18 mmHg and 14.76 ± 4.14 mmHg, respectively, and the mean difference was −2.56 (95% CI, −3.80 to −1.32; P < 0.001). The study concluded that primary trabeculectomy was more effective in lowering IOP, as well as preventing disease progression compared to the primary medical treatment in patients with advanced disease[4].

Minimal Invasive Treatment vs Trabeculectomy

Although the global ophthalmological community still consider trabeculectomy being the gold standard surgical treatment for glaucoma, substantial effort has been made during the last decade to create a more innovative surgical procedure that is as effective as trabeculectomy, but with a better safety profile[6]. One such procedure is the microinvasive glaucoma surgery (MIGS) which is an innovative, subconjunctival draining using minimally invasive glaucoma device (microshunt) that creates a posterior bleb in the upper subconjunctival space. This reduces the inflammation and the rate of encapsulation during the surgery[6]. The efficacy and safety of microshunt and trabeculectomy in patients with advanced OAG was assessed in a single-centre study by Fili *et al*., (2022). Interestingly, 300 patients with moderated to advanced OAG were treated with either MicroShunt (n=150 eyes) or trabeculectomy (n=150 eyes).

During the 12-month follow-up period, 81.3% patients treated with microshunt showed a reduction in IOP by >20% without glaucoma eye drops, compared to 94% of patients treated with trabeculectomy. Strikingly, the number of topical medications administered 12 months after ocular surgery was 0.4±0.8 in group treated with microshunt compared to 0 in patients treated with trabeculectomy. Thus, the findings from this study suggested that microshunt was non-superior to trabeculectomy at reducing IOP after 12 months. In addition, patients undergone trabeculectomy had a better absolute success rates after 12 months compared to microshunt (**Figure 2**)[6]. Despite newer surgical advancement for advanced glaucoma is still emerging, trabeculectomy remains vital since it remains the most commonly performed surgical procedure for medically uncontrolled glaucoma. Furthermore, thanks to peri- and postoperative modifications in recent years[7], trabeculectomy has now become more safer and has improved surgical outcomes in patients with advanced glaucoma compared to the past.

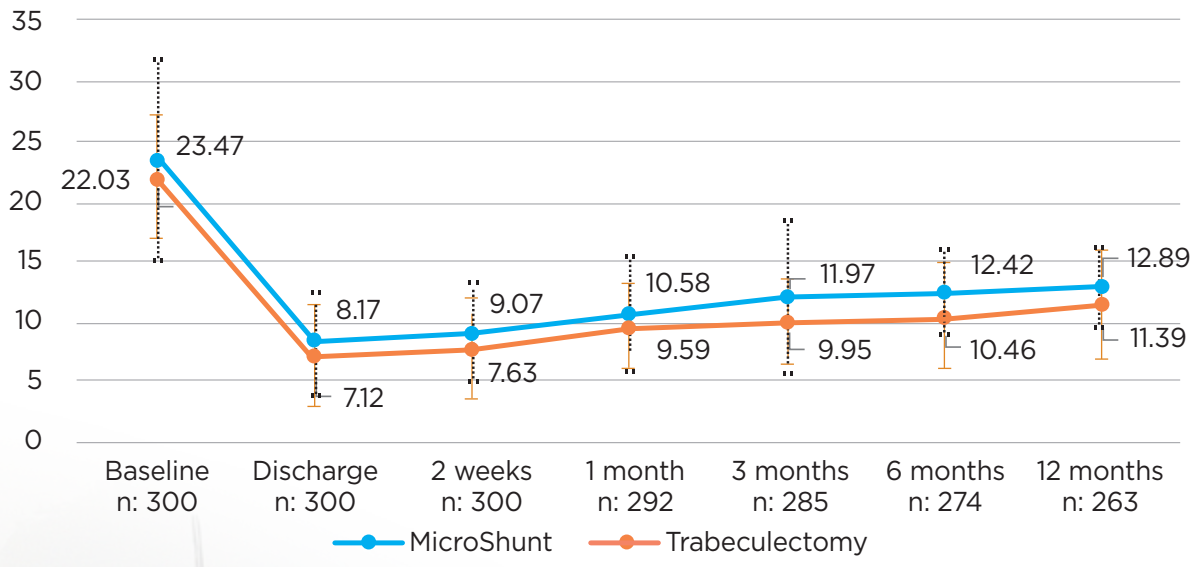
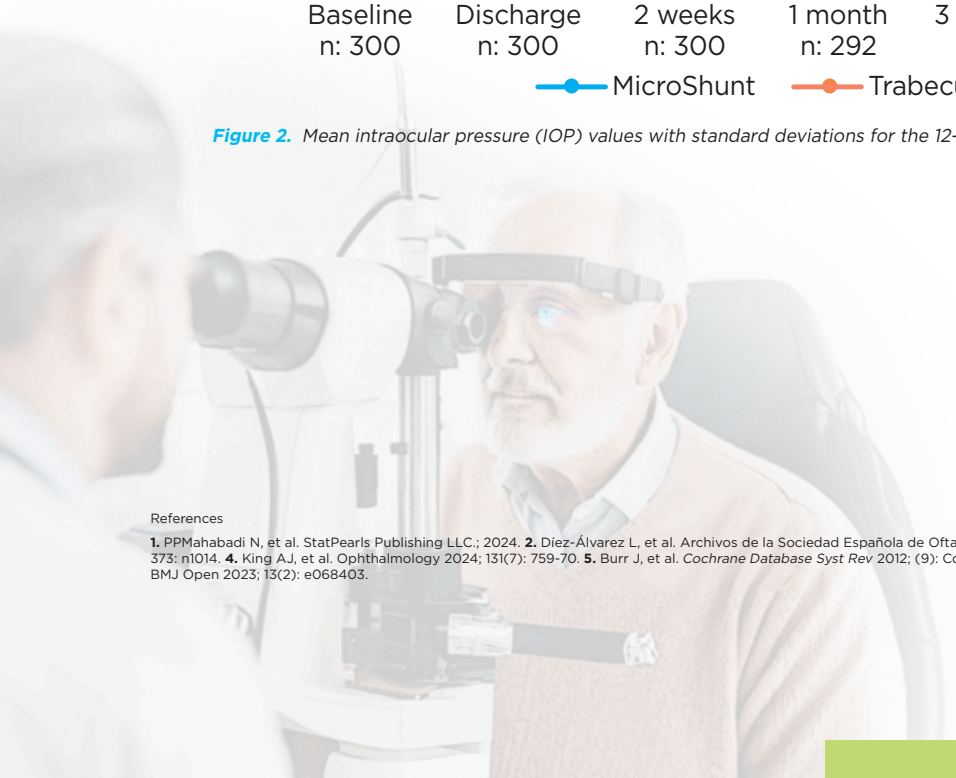


Figure 2. *Mean intraocular pressure (IOP) values with standard deviations for the 12-month follow-up period[6].*



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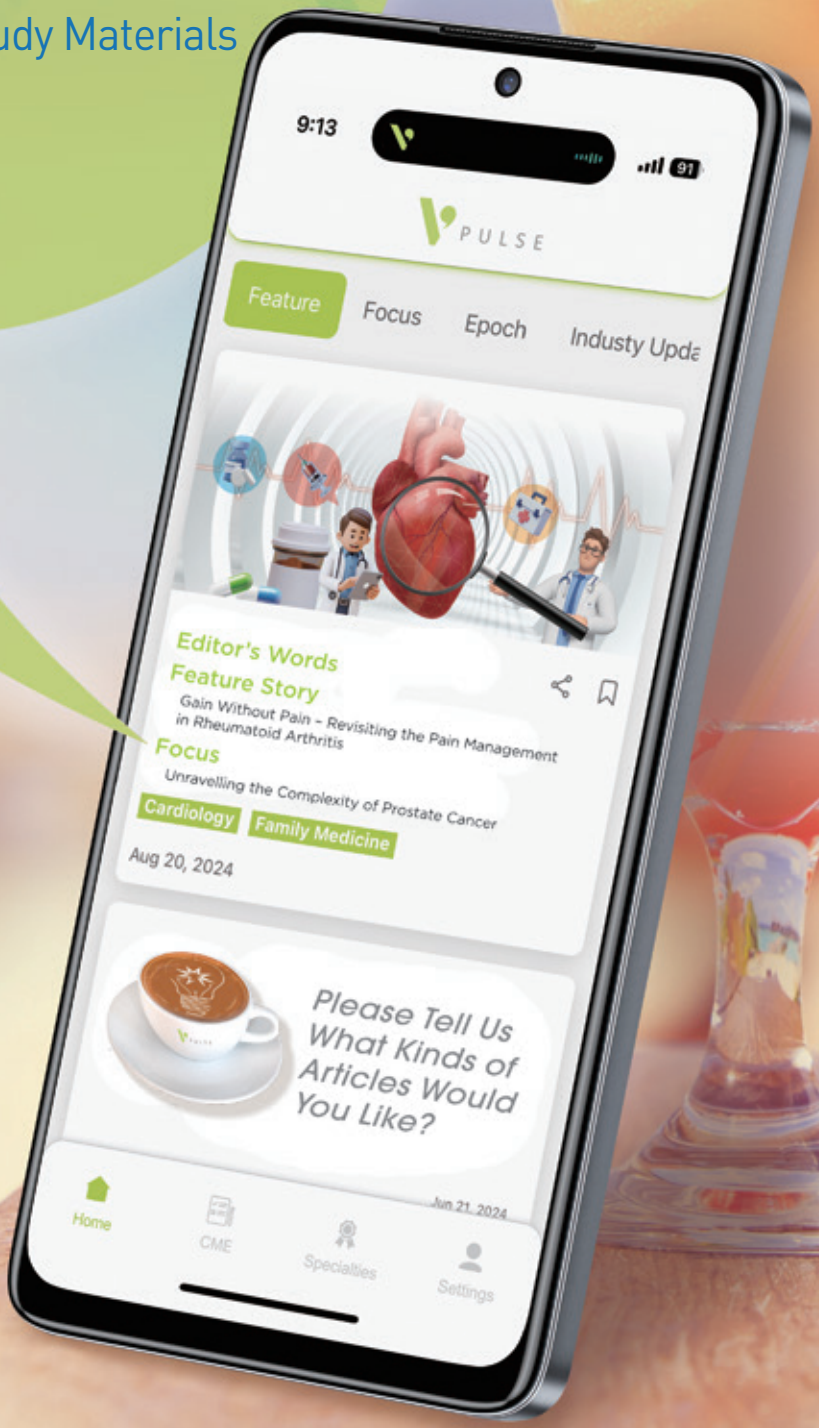

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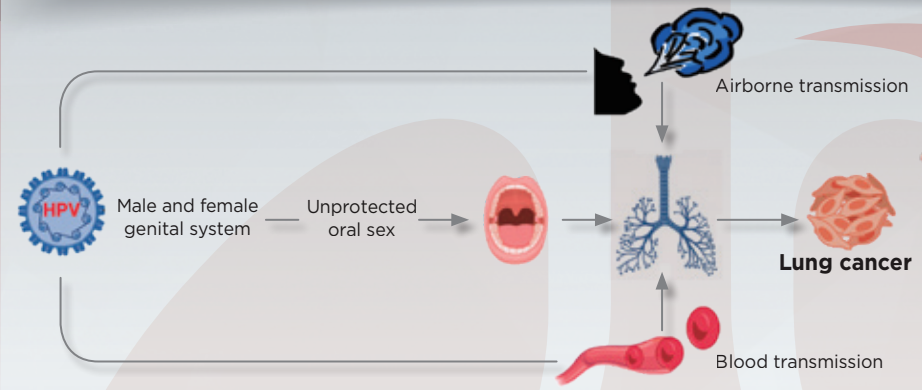
The Complexity of HPV and Lung Cancer – a Snapshot of Mechanistic Understandings

by Jasmine Lai

Lung cancer is the second-most common cancer diagnosis and the leading cause of cancer-related mortality worldwide. Over the years, an alarming reversal of epidemiological trends has occurred: smoking rates and lung cancer in males has steadily declined in males and drastically risen in women and never-smokers, particularly in Asia[1]. Interestingly, high-risk human papillomaviruses (HPVs) have been identified in non-small cell lung cancer (NSCLC), though the extent of its role in this complex and molecularly heterogenous disease has remained controversial[2]. Amidst the mounting pressure to uncover new explanations behind the rise in lung cancer cases and the potential role of HPV in NSCLC, what are the mechanisms underlying their interaction?

HPV entry into the lungs can occur through multiple routes[3,4]



In addition to HPV's conventional routes of entry, Carpagnano *et al.* (2011) were able to detect HPV in the exhaled breath condensate in 94% of patients diagnosed with NSCLC that were included in the study

Diagram adapted from Nachira et al. 2024[4].

HPV-induced carcinogenesis may synergise with tobacco smoke[4]

Independent carcinogenesis:

HPV E6/7 oncoprotein overexpression

- Cell proliferation, immortalisation, oxidative stress, DNA damage, cell cycle blockade
- Epithelial–mesenchymal transition
- Angiogenesis
- EGFR mutation

Dependent carcinogenesis:

Both HPV and cigarette smoke enter cells through the squamocolumnar junctions

- Inhaled cigarette smoke increases E6/7 activity
- E6/7 increases cell sensitivity to smoke
- Inhaled cigarette smoke impairs the body's immune responses against HPV

HPV can also integrate into the genome and alter gene expression in nearby sites

HPV may be cleared spontaneously after inducing carcinogenesis[5]

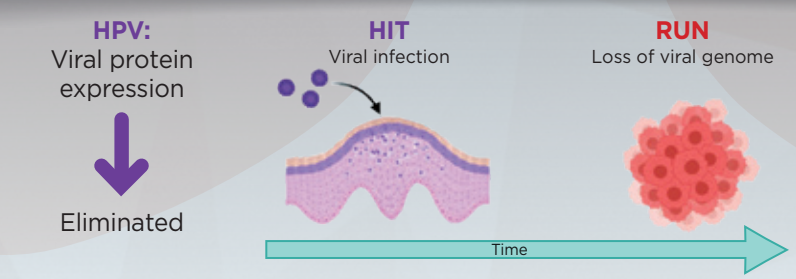


Diagram adapted from Fernandes et al. 2022[5].

Abbreviations:

EBC, exhaled breath condensate; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; PBMC, peripheral blood mononuclear cells

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to restore immune homeostasis with favorable safety[6]

ZERO CMV infection[6]
<4% grade ≥3 cytopenias[6]

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Suggested Systemic Agent

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INDICATION[1]

REZUROCK® (belumosudil) is indicated for the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.

* Based on a final analysis by the FDA (n=65)
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cGVHD, chronic graft-versus-host disease; CMV, cytomegalovirus; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network®; ORR, overall response rate; ROCK2, rho-associated coiled-coil–containing protein kinase-2.

References: 1. REZUROCK® Hong Kong Prescribing Information. 2. Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Proc Natl Acad Sci USA. 2014;111(47):16814-16819. 3. Flynn R, Paz K, Du J, et al. Blood. 2016;127(17):2144-2154. 4. Data on file 1. Kadmon Pharmaceuticals, LLC; 2021. 5. Data on file 2. Kadmon Pharmaceuticals, LLC; 2020. 6. Cutler C, Lee SJ, Arai S, et al. Blood. 2021;138(22):2278-2289. 7. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Hematopoietic Cell Transplantation (HCT) Version 3.2023 - October 9, 2023.

Abbreviated Prescribing Information
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Clinical Trial Snapshot:
On the PATH Towards an Approved Treatment: the Value of Drug Repurposing

by Jasmine Lai

Thalidomide's tragic history, teratogenic toxicities, and role in restructuring regulatory bodies are forever etched in the annals of medicine[1]. However, the discovery of its antiangiogenic and immunomodulating properties have since led to a resurgence of repurposing thalidomide, particularly in haemotological cancers, as well as in developing less toxic analogues, such as pomalidomide[2,3]. Pomalidomide has also been used to treat hereditary hemorrhagic telangiectasia (HHT), a rare disease currently with no approved treatment[4]. However, this may be about to change since the results from a phase 2 trial showed promising findings, marking a step towards a validated HHT treatment[5].

PATH-HHT trial: Phase 2[5]

HHT Background

- HHT is the second most common inherited bleeding disorder
- Epistaxis occurs in >95% of patients and results in iron-deficiency anaemia
- Complications, psychiatric comorbidities and poor health-related quality of life or life expectancy are common

Objective

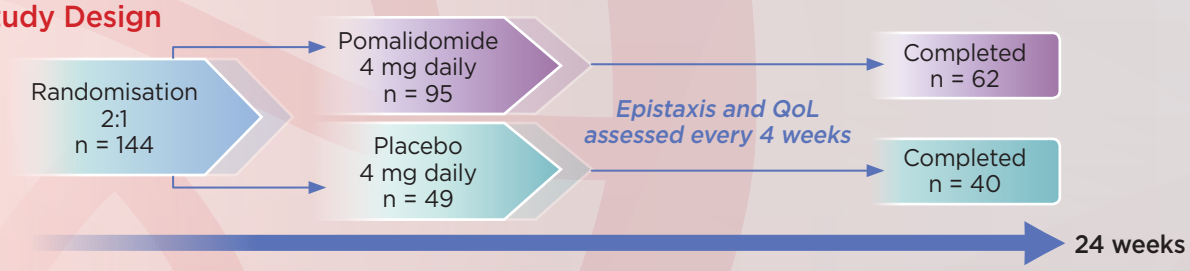
- Determine if oral pomalidomide effectively treats HHT and evaluate its disease-modifying effects in HHT

Patient Inclusion Criteria

Adult patients with:

- Epistaxis Severity Score ≥3 within the 3 months prior to screening
- Anaemia at screening/received iron infusions or red-cell transfusions in the previous 6 months

Study Design

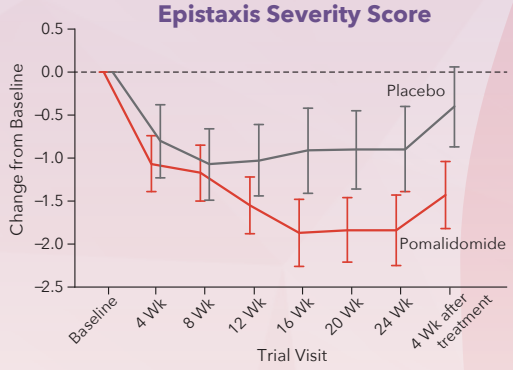


Trial enrolment closed early after a planned interim analysis met the prespecified threshold for efficacy

Results

Primary outcome:

Epistaxis Severity Score



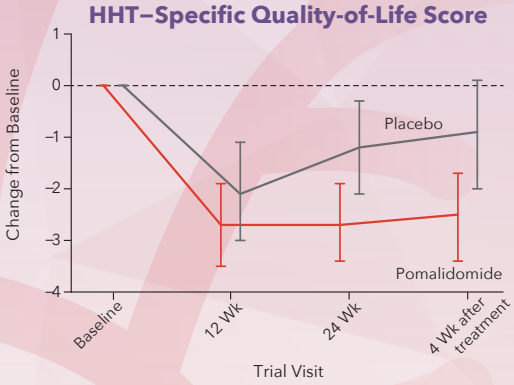
Mean difference between pomalidomide and placebo: −0.94 points

95% [CI], −1.57 to −0.31; P = 0.004)

Exceeds the minimally important difference: 0.71

Key secondary outcome:

HHT–Specific Quality-of-Life Score



P<0.001 not met

Conclusion and Future Perspectives

- Pomalidomide shows efficacy in reducing HHT-related epistaxis in the PATH-HHT trial
- Small improvements in QoL experienced by patients suggests that further long-term trials are warranted
- Additional studies can further evaluate whether pomalidomide demonstrates similar effects in patients with gastrointestinal bleeding or with pulmonary, liver, or brain arteriovenous malformations

Abbreviations:

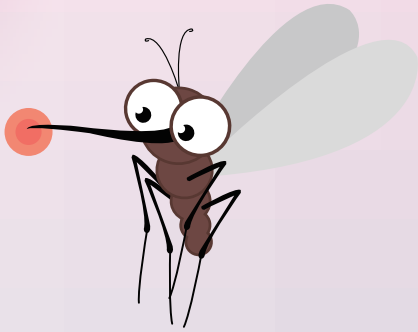
CI, confidence interval; HHT, hereditary hemorrhagic telangiectasia; QoL, quality of life.

References:

1. Rajkumar SV. Mayo Clinic Proceedings 2004;79:899–903. **2.** Kale VP et al. Semin Cancer Biol 2021;68:242–248. **3.** Ugur MC et al. J Clin Med 2024;13:5404. **4.** Al-Samkari H. Blood 2024;144:940–954. **5.** Al-Samkari H et al. NEJM 2024;391:1015–1027.

30-50% 日本腦炎倖存者有嚴重後遺症

持續出現嚴重神經、認知及行為等問題[1]



世衛強烈建議接種日本腦炎疫苗以預防感染[2]

九個月大或以上兒童已可接種日本腦炎疫苗[3]

致命腦炎禍害深 主動預防唔好揾 快搵醫生去「針針」

本內容由裕利醫藥提供以作教育用途，以上資料只供參考，詳情請向醫生查詢。

參考資料: 1. Simon LV et al. Japanese Encephalitis. In: StatPearls [Internet]. StatPearls Publishing; 2023. Accessed March 27, 2024. https://www.ncbi.nlm.nih.gov/books/NBK470423/ 2. Japanese encephalitis. Accessed March 27, 2024. https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis 3. Imojev. Prescribing Information. CCDSv.10. TGA ref. Sep 2016.pdf.

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SUBSTIPHARM BIOLOGICS

HK-PM-Substipharm-IMOJEV-IDA-PA-000001-06-2024

Relieving Maternal Anxiety During and After the Process of Childbirth with Music Therapy[1]

Maternal anxiety is prevalent, with rates ranging from 18.2% in early pregnancy to 24.6% in late pregnancy. The condition has been reported to be associated with negative consequences, including premature birth, lower birth weight, postpartum depression, diminished prenatal bonding, and etc. Given the benefits of music on physical, emotional, and spiritual well-being of pregnant women, the potential of music as a readily available, affordable, and non-pharmacological intervention against maternal anxiety has attracted researchers' interest. A recent clinical study involved 217 pregnant women by Ji et al. (2024) demonstrated that pregnant women who exposed to music during labour exhibited reduced scores of State Anxiety Inventory (STAI), both during the active time and two hours after giving birth compared to control group. At the first stage of labour, pregnant women in the music group experienced dramatically reduced score of pain in active phase and Edinburgh postnatal depression scale at discharged from the hospital. Thus, receptive music therapy in obstetric care can be an effective tool in preventing anxiety-induced complications.

Protective Effect of Bone Morphogenetic Protein 9 Against Myocardial Infarction

Bone morphogenetic proteins (BMPs) were originally identified as inducers of ectopic bone growth and cartilage formation, whereas emerging literature reported the multiple functions of these growth factors, including regulating cell growth, differentiation, and apoptosis of various cell types. In particular, BMP-9 is expressed in the adult liver by nonparenchymal cells as well as in the septum and spinal cord of mouse embryos[2]. Duan et al. (2024) recently reported the potential protective effects of BMP-9 against myocardial infarction (MI). Based on expressional profiles of BMP-9 in cardiac tissues and plasma samples, circulating BMP-9 and its cardiac levels are markedly increased in humans and mice with MI and are negatively associated with cardiac function. While BMP-9 deficiency exacerbates MI-related changes in mice models, replenishment of BMP-9 significantly attenuates these adverse effects. The research team further demonstrated that BMP-9 improved lymphatic drainage function and hence reduced cardiac oedema. Interestingly, the results also indicated that BMP-9 increased the expression of mitochondrial DECR1 (2,4-dienoyl-CoA reductase 1) which promotes cardiac mitochondrial bioenergetics and mitigates MI-induced cardiomyocyte injury[3]. Therefore, it is likely that BMP-9 protects against MI by improving lymphatic drainage function and triggering DECR1-mediated mitochondrial bioenergetics.

Serological Screening for Atrophic Gastritis by Assessing Postprandial Level of Gastrin-17

Atrophic gastritis is a basic precancerous disease of the stomach and serological markers have been demonstrated effective for screening for atrophic gastritis and, in turn, preventing gastric cancer. Recently, a clinical study involving 169 patients with atrophic gastritis evaluated the effectiveness of assessing postprandial levels of gastrin-17 (G17) for screening atrophic gastritis. In the study, the histological standard of 5 biopsies of the gastric mucosa was used to assess the sensitivity of G17 in detecting gastric mucosal atrophy. Also, the morpho-functional relationships between the detected histological degree of gastric mucosal atrophy and the serological levels of G17 and pepsinogen-1 (PG1) were compared. The sensitivity of postprandial G17 was 62.2% for serological levels of G17 and 100% for serological G17 for the detection of mono-focal severe atrophic gastritis[4]. Thus, postprandial G17 can be recommended for dynamic monitoring of atrophic gastritis after treatment.

The 1-year Follow-up on the Transplantation of Chemically Induced Pluripotent Stem-cell-derived Islets in a Type 1 Diabetes Patient

Type 1 diabetes mellitus (T1D) is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells. Practically, management of T1D requires multiple daily insulin injections, insulin pump therapy, or the use of an automated insulin delivery system, as well as glucose monitoring, preferably with a continuous glucose monitor[5]. Wang et al. (2023) performed the first-in-human phase I clinical trial on transplanting chemically induced pluripotent stem-cell-derived islets (CiPSC islets) for treating T1D. The autologous pluripotent stem cells of a T1D patient were induced to differentiate into islet-like cells. After passing all quality control and preparation procedures, the cell suspension was implanted underneath the abdominal anterior rectus sheath. The 1-year follow-up results of the case has been published recently. Remarkably, the patient achieved sustained insulin independence starting 75 days post-transplantation. The patient's time-in-target glycaemic range increased from a baseline value of 43.18% to 96.21% by month 4 post-transplantation, accompanied by a decrease in glycated haemoglobin. At 1 year, the clinical data met all safety and efficacy clinical endpoints[6]. Based on the findings, CiPSC-islet transplantation appears to be an effective strategy countering T1D, and further clinical studies are warranted.

Caffeine Intake Is Unlikely to Cause Erectile Dysfunction

Erectile dysfunction (ED) is the inability to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse, which substantially reduces the quality of life for patients and their partners. While ED prevalence increases with age, various co-morbidities such as depression, obesity, lack of exercise, diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease, are associated with the condition[7]. Caffeine has been reported to associate with multiple physiological effects on vascular function and hormonal balance that might influence sexual function. Nonetheless, the meta-analysis of 4 cohort studies comprised 51,665 male cohort members by Karimi et al. (2024) revealed no significant relationship between coffee consumption and the risk of ED (relative risk [RR]: 0.94, p=0.999)[8].

References

1. Ji et al. *Front Psychiatry* 2024; 15. DOI:10.3389/FPSYT.2024.1429999. **2.** David et al. *Circ Res* 2008; 102: 914–22. **3.** Duan et al. *Circulation* 2024. DOI:10.1161/CIRCULATIONAHA.123.065935. **4.** Kotelevets et al. *World J Gastrointest Endosc* 2024; 16: 462–71. **5.** Type 1 Diabetes - StatPearls - NCBI Bookshelf. **6.** Wang et al. *Cell* 2024; 0. DOI:10.1016/J.CELL.2024.09.004. **7.** McMahon et al. *Med J Aust* 2019; 210: 469–76. **8.** Karimi et al. *J Health Popul Nutr* 2024; 43: 154.

by Dr. Mohsin Roshan

AQUIPTA®

(Atogepant)

ABBVIE

HK Reg. No. HK-68287 (03 Jul, 2024) & HK-68288 (03 Jul, 2024)

Composition:[1]

Aquipta® (Atogepant) is an orally administered, small molecule, selective calcitonin gene-related peptide (CGRP) receptor antagonist that blocks the binding of the CGRP to the receptor and antagonizes CGRP receptor function. CGRP is a neuropeptide that has been associated with migraine pathophysiology. It is available in 10 mg and 60 mg tablet forms.

Indication:[1]

Aquipta® (Atogepant) tablet is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

ANAGRELIDE SANDOZ®

(Anagrelide hydrochloride)

NOVARTIS

HK Reg. No. HK-68231

Composition:[2]

ANAGRELIDE SANDOZ® (anagrelide hydrochloride) is an inhibitor of cyclic AMP phosphodiesterase III. It is available in 0.5 mg hard capsule.

Indication:[2]

ANAGRELIDE SANDOZ® (anagrelide hydrochloride) is indicated for the reduction of elevated platelet counts in at risk essential thrombocythemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

AMOROLFINE®

(Amorolfine hydrochloride)

NOVARTIS

HK-68364 (09 Sept, 2024)

Composition:[3]

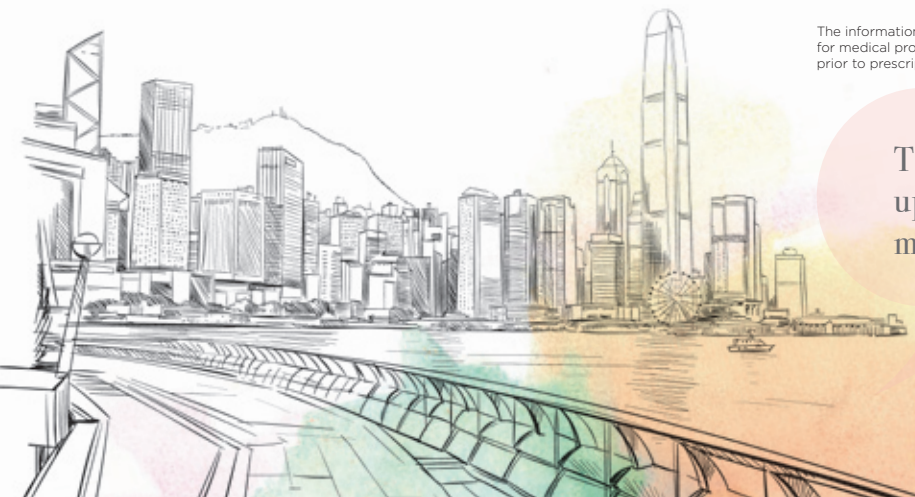
AMOROLFINE® (amorolfine hydrochloride) is a topical antimycotic. Amorolfine belongs to a new chemical class, and its fungicidal action is based on an alteration of the fungal cell membrane targeted primarily on sterol biosynthesis. The ergosterol content is reduced, and at the same time unusual sterically nonplanar sterols accumulate.

Indication:[3]

AMOROLFINE® (amorolfine hydrochloride) is used to treat mild cases of distal and lateral subungual onychomycoses caused by dermatophytes, yeasts and moulds limited up to 2 nails.

References

1. AQUIPTA® (atogepant) EU Summary of Product Characteristics. August 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/aquipta. Accessed November 2023. **2.** Anagrelide Sandoz 0.5 mg hard capsule - Summary of Product Characteristics (SmPC) - (emc). https://www.medicines.org.uk/emc/product/10094/smpc#gref. **3.** Amorolfine 5% w/v Medicated Nail Lacquer (Legal category P) - Summary of Product Characteristics (SmPC) - (emc). https://www.medicines.org.uk/emc/product/7414/smpc#gref.



To keep pace with drug information updates and discover newly launched medicines in Hong Kong.

Delay the Renal Deterioration with JINARC® in ADPKD[1,2]

Effectively slow kidney growth and renal function decline[1]

Slower decline in eGFR at 1 year in patients with later-stage ADPKD vs placebo (1.27ml/min/1.73m^2 net difference; 95% CI, 0.86 to 1.68; P<0.001)[2]

Effectively reduced incidence of kidney pain, kidney stone, urinary tract infection, and haematuria[3]

ERA WGIKD / ERKNeT Position Statement 2021

JINARC® is recommended in:

Adult ADPKD patients ≤55 years of age with an eGFR ≥25ml/min/1.73m^2.^[4]

Start as soon as rapid disease progression determined in patients ≥ 18 years of age.[4]

^Who have demonstrated or who are likely to have rapidly progressive disease based on a hierarchical decision algorithm in 2021 consensus statement by ERA, WGIKD, ERKNet and PKD International.

ADPKD: autosomal dominant polycystic kidney disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; ERA: European Renal Association; ERKNet: European Rare Kidney disease reference NETwork; PKD: polycystic kidney disease; WGIKD: Working Group on Inherited Kidney Disorders.

References:
1. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012 Dec 20;367(25):2407-2418. 2. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, Ouyang J, McQuade RD, Blais JD, Czerwiec FS, Sergeyeva O; REPRISE Trial Investigators. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2017 Nov 16;377(20):1930-1942. 3. Casteleijn NF, Blais JD, Chapman AB, Czerwiec FS, Devuyst O, Higashihara E, Leliveld AM, Ouyang J, Perrone RD, Torres VE, Gansevoort RT; TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4 Trial Investigators. Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial. Am J Kidney Dis. 2017 Feb;69(2):210-219. 4. Müller RU, Messchendorp AL, Birn H, Capasso G, Cornec-Le Gall E, Devuyst O, van Eerde A, Guirchoun P, Harris T, Hoorn EJ, Knoers NVAM, Korst U, Mekahli D, Le Meur Y, Nijenhuis T, Ong ACM, Sayer JA, Schaefer F, Servais A, Tesar V, Torra R, Walsh SB, Gansevoort RT. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. Nephrol Dial Transplant. 2022 Apr 25;37(5):825-839.

Abbreviated Prescribing Information
JINARC (tolvaptan) 15mg, 30mg, 15mg + 45mg, 30mg + 60mg, 30mg + 90mg tablets.
INDICATION: indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease.
DOSAGE: twice daily in split dose regimens: initially 60mg/day as 45 mg + 15 mg (45 mg taken upon waking & prior the morning meal and 15 mg taken 8 hours later). Titrate upward to 90mg/day (60 mg + 30 mg) and then to a target dose of 120mg/day (90 mg + 30 mg), if tolerated, with at least weekly intervals between titrations. Based on tolerability, down-titrate and maintain on the highest tolerable dose. Take morning dose at least 30 min before breakfast. Take 2nd dose with or without food. Swallow whole with a glass of water, do not chew or crush. Avoid grapefruit juice. **CONTRAINDICATION:** Hypersensitivity to this product, or to benzazepine or its derivatives; Elevated liver enzymes and/or signs or symptoms of liver injury before initiation of treatment; Anuria; Volume depletion; Hypernatraemia; Patients who cannot perceive or respond to thirst; Pregnancy and breastfeeding. **WARNINGS AND PRECAUTIONS:** Idiosyncratic hepatic toxicity. Perform blood testing for hepatic transaminases & bilirubin prior to initiation of treatment, continuing mthly for 18 month & at regular 3-monthly intervals thereafter. Monitor for symptoms that may indicate liver injury. Drink water or other aqueous fluids to avoid excessive thirst or dehydration. Monitor volume, fluid & electrolyte status. Urinary output must be secured. Correct hyponatraemia or hypernatraemia before initiation of treatment. Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. Exclude pseudohyponatraemia in DM patients prior & during treatment. May cause hyperglycaemia. Evaluate uric acid concentration prior to initiation of therapy & as indicated during treatment based on symptoms. Reversible reduction in GFR. Discontinue treatment if renal insufficiency progresses to CKD stage 5. Severe hepatic impairment. Minor influence on the ability to drive or use machines. Not recommended in the paediatric age group. **ADVERSE REACTIONS:** Very common - polydipsia; headache, dizziness; diarrhoea, dry mouth; nocturia, pollakiuria, polyuria; fatigue, thirst. Common - dehydration, hypernatraemia, decreased appetite, hyperuricaemia, hyperglycaemia; insomnia; palpitations; dyspnoea; abdominal pain, abdominal distension, constipation, dyspepsia, GERD; abnormal hepatic function; rash, pruritus; muscle spasms; asthenia; increased ALT & AST, decreased weight. **DRUG INTERACTIONS:** Increased exposure with moderate or strong CYP3A4 inhibitors. Decreased exposure & efficacy with potent CYP3A4 inducers. Higher risk for developing hypernatraemia with medicinal products that increase serum Na concentration. Potential to lead to severe dehydration with loop & thiazide diuretics. Increased steady state concentration of digoxin. Use with caution when co-administered with OATP1B1 & OATP1B3 substrates (e.g. statins), OAT3 substrates (e.g. methotrexate, ciprofloxacin), BCRP substrates (e.g. sulfasalazine) or OCT1 substrates (e.g. metformin). Possible attenuation of effect of vasopressin analogues e.g. desmopressin. **Please see full Prescribing information for details.** (Ref: HKPI Revised May 2020; Last Update: Oct 2022)

HKOP-JIN-202309-001

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References
1. Garneata L, Stancu A, Dragomir D et al. Ketoanalogues-supplemented Vegetarian Very Low Protein Diet and CKD Progression. J Am Soc Nephrol 2016;27(7):2164-2176. **2.** Brunori G, Viola BF, Parrinello G et al. Effi cacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. Am J Kidney Dis 2007;49:569-580. **3.** Shah AP, Kalantar-Zadeh K, Kopple JD. Am J Kidney Dis. 2015;65:659-673 **4.** Mircescu G, Garneata L, Stancu SH, Capusa C. Effects of a Supplemented Hypoproteic Diet in Chronic Kidney Disease. J Ren Nutr. 2007;17(3):179-188. **5.** Cupisti A, D'Alessandro C, Gesualdo L, et al. Non-Traditional Aspects of Renal Diets: Focus on Fiber, Alkali and Vitamin K1 Intake. Nutrients. 2017 Apr 29;9(5). pii: E444. doi: 10.3390/nu9050444.

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