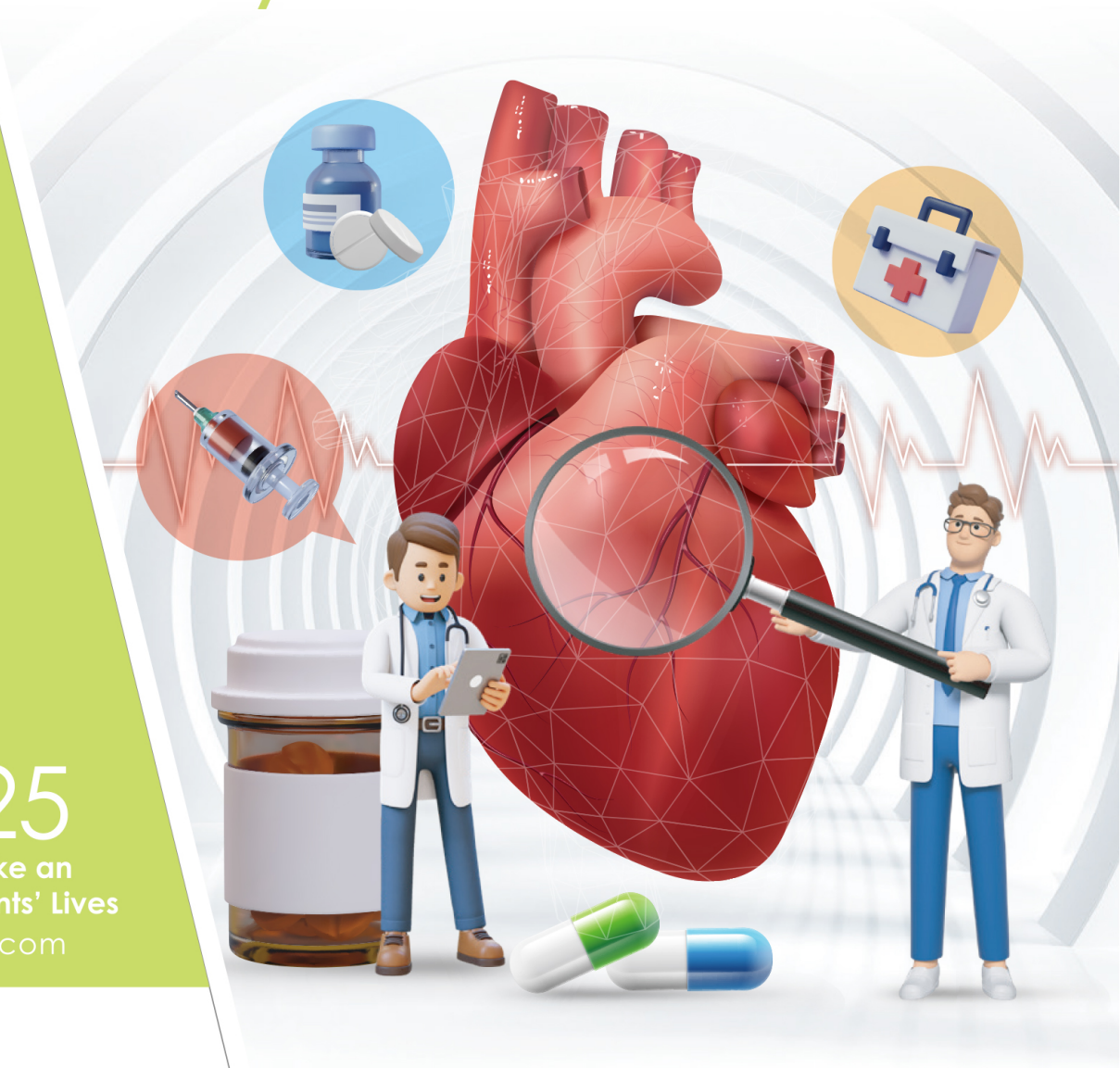
PULSE

What's New in Coronary Artery Disease?



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Accredited Articles Inside

ONUREG® (azacitidine)

FRONTLINE ORAL AML MAINTENANCE THERAPY PROVEN TO EXTEND OVERALL SURVIVAL[1]

SEE AML TREATMENT IN A DIFFERENT LIGHT

ONUREG® provided ~10 months longer OS
compared with placebo in patients with AML in first remission following induction therapy with or without consolidation[1]

24.7 MONTHS with ONUREG® (95% CI: 18.7, 30.5)	VS	14.8 MONTHS with PLACEBO (95% CI: 11.7, 17.6)

HR 0.69 (95% CI: 0.55, 0.86; *P*=0.0009)[2]

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]

Reference: 1. Wei AH, Döhner H, Pocock C, et al. Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission. N Engl J Med. 2020;383(26):2526-2537. 2. ONUREG® Hong Kong Prescribing Information July 2023

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***INVEGA HAFYERA® compared with INVEGA TRINZA®[3]**

References: 1. INVEGA HAFYERA® Hong Kong Prescribing Information P01. **2.** Janssen Announces U.S. FDA Approval of INVEGA HAFYERA™ (6-month paliperidone palmitate), First and Only Twice-Yearly Treatment for Adults with Schizophrenia. 2021. Available at: https://www.jnj.com/media-center/press-releases/janssen-announces-u-s-fda-approval- of invega-hafyera-6-month-paliperidone-palmitate-first-and-only-twice-yearly-treatment-for-adults-with-schizophrenia. **3.** Najarian D et al. Int J Neuropsychopharmacol 2022:25; 238–251. **4.** INVEGA SUSTENNA® Hong Kong Prescribing Information P11.

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EDITOR'S WORDS

Dear Reader,

Although a decreasing trend in mortality from coronary artery disease (CAD) has been observed in recent years, the burdens of the disease on individuals and healthcare systems are still significant, accounting with substantial medical expenses and reduced quality of life (QoL). Thus, implementing preventive measures of CAD and cost-saving strategies are essential. Concerning the risk factors of CAD, the role of psychosocial factors are noteworthy, yet often overlooked. Therefore, the association between psychosocial factors and the development of CAD will be highlighted in the Feature Story. Moreover, the advancement in diagnosis, cutting-edge treatment including medications and surgical procedures for CAD, will also be covered. In particular, the use of artificial intelligence (AI) in optimising the outcomes of patients with CAD will be discussed.

In the current Focus section, the breakthrough in management of treatment-resistant depression (TRD) will be discussed. Undoubtedly, major depressive disorder (MDD) is a prevalent and challenging psychiatric disease. A considerable proportion of MDD patients show only modest response to antidepressant treatment. While some of these cases are in fact pseudo-resistance, many of them suffer from TRD. Apart from the conventional electroconvulsive therapy (ECT), recent clinical data reported the promising outcomes in TRD patients yielded by esketamine treatment. Hence, expert opinions and existing clinical evidence on the benefits of esketamine in controlling TRD will be reviewed.

In addition to the thematic topics, updates on the pharmacologic management of relapsed/refractory multiple myeloma (RRMM), and giant cell arteritis (GCA) are highlighted in the Industry Updates. On the other hand, the innovations in gene therapy, and the roles of matrix metalloproteases (MMPs) in the development of tendinopathy and its clinical implications will be discussed in the Epoch section.

Hope you enjoy this issue!

Dr. Roy Yuen-chi Lau
PhD, DBA, MPH, MMedSc, MA, BSc,
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Editor-in-Chief

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by Dr. Roy Lau

What's New in Coronary Artery Disease?

Dr. Roy Yuen Chi Lau, PhD, DBA
Editor-in-Chief, V·Pulse

Dr. Mohsin Roshan, MSc, MD
Doctor at the National Health Services (NHS), United Kingdom (UK)

Coronary artery disease (CAD) is a significant health challenge, imposing substantial burdens on individuals and healthcare systems worldwide. Notably, in Hong Kong, 1.6% of those aged 15 or above are reported as doctor-diagnosed CAD, with a higher prevalence seen in males (2.1%) compared to females (1.2%). The prevalence increases with age, from 0.1% in those aged 15-24 to 7.7% for those aged 85 or above[1]. Thanks to the collaborative efforts by researchers, healthcare professionals, and government bodies, advancements in diagnostics, cutting-edge treatment including medications and surgical procedures for CAD are emerging. In addition, a better understanding on the risk factors associated with CAD facilitates more effective lifestyle modifications and cardiac rehabilitation leads to improved patients' outcomes and overall quality of life (QoL).

CAD Remains a Global Health Challenge

Although mortality has decreased in recent decades, CAD remains one of the leading causes of mortality and morbidity in developed countries. Stark *et al*. (2024) recently reported that the global age-standardised prevalence of CAD was 3,605 (95% CI: 2,892-4,454) per 100,000 in 2022, an 18% decrease since the 1990s. Central Europe, and Eastern Europe, as well as Central Asia accounted for the highest age-standardised prevalence of CAD while South Asia having the lowest[2].

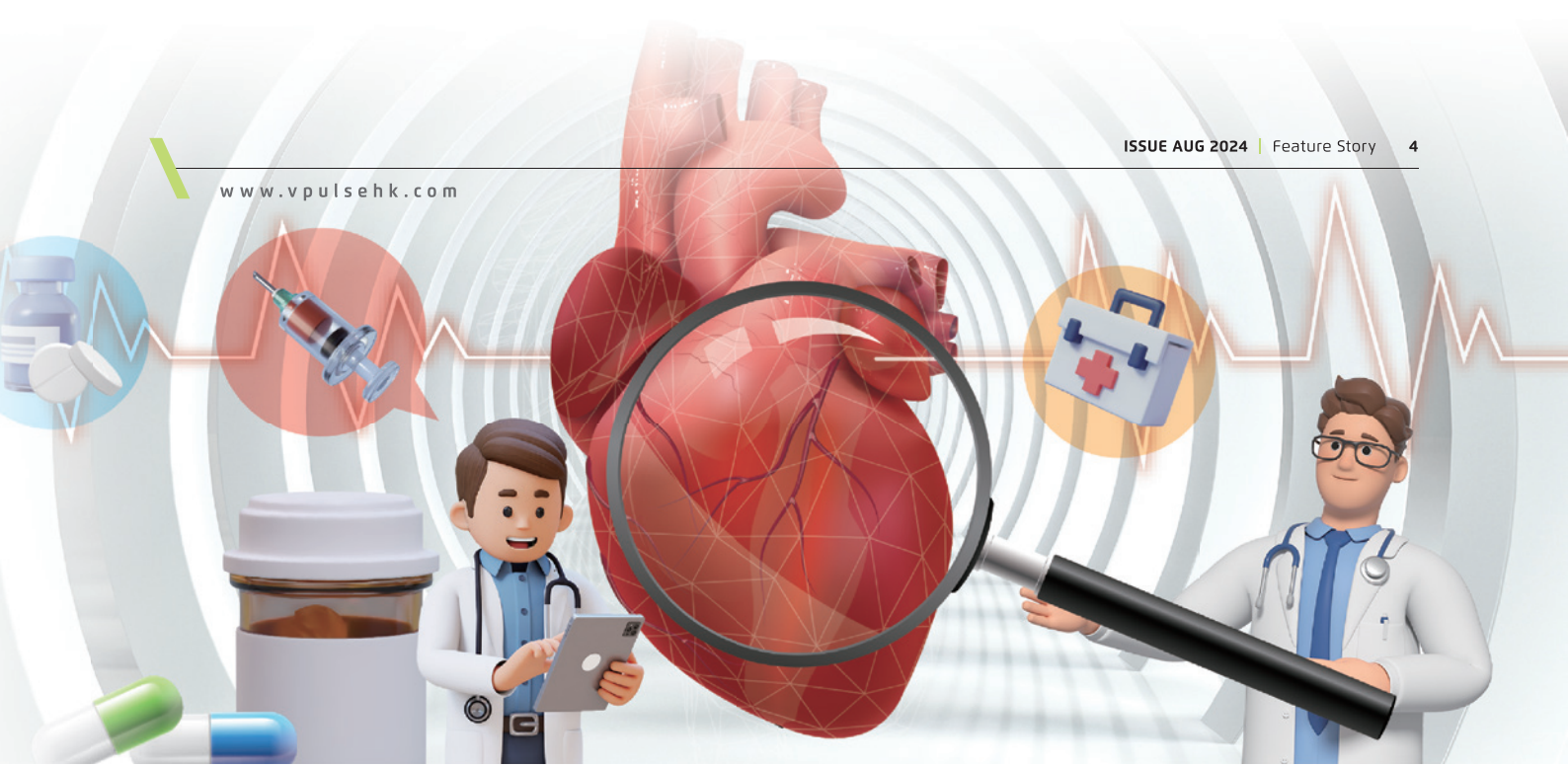
In Hong Kong, according to the Centre for Health Protection (CHP), CAD accounted for 58.8% of heart disease-related deaths in 2020, whereas the age-standardised death rates due to CAD accounted for 30.5 in male and 11.9 in female per 100,000 standard population. Align with the global trend, a gradual decrease in age-standardised death rate of CAD was observed since 1981 (**Figure 1**)[1].

While CAD potentially leads to adverse cardiovascular (CV) events, such as myocardial infarction (MI) and stroke, the economic burden of CAD is undoubtedly substantial, which includes direct costs on hospitalisation and medication, as well as the loss of productivity. For instance, a local study involving 89 patients with newly diagnosed stable CAD by Lee *et al*. (2013) reported that the mean first-year total direct medical cost of newly diagnosed stable CAD per patient was US$11,477 (HK$89,521). Hospitalisation accounted for 29.2% of the total cost. The results further highlighted that the total cost for patients who underwent invasive coronary procedure was significantly higher than those treated medically alone (HK$115,339 vs HK$47,744, p<0.001)[3]. Thus, implementing preventive measures of CAD and cost-saving strategies are essential.

Be Aware of the Psychosocial Risk Factors of CAD

It is well-established that non-modifiable intrinsic risk factors, including age, sex, family history, and ethnicity are associated with the development of CAD. In contrast, lifestyle habits, such as physical activity, amount of good-quality sleep, dietary patterns, and smoking behaviour, are considered as modifiable factors for CAD[4]. Controlling these risk factors may help lower the risk of developing heart disease and may improve the overall health and wellbeing.

Aside from physiological and lifestyle risk factors, the role of psychosocial factors in relation to the development of CAD is also noteworthy. Albus (2010) evaluated the effects of psychosocial factors such as low socio-economic status, lack of social support, stress at work and family life, depression, anxiety, as well as hostility has on the risk of developing CAD as well as clinical course and prognosis of the disease[5]. Remarkably, it was reported that the psychosocial risk factors may actually hinder treatment adherence and impede the efforts to control modifiable lifestyle risk factors[6].



A meta-analysis of 23 reports included 4,628 CAD and 3,002 stroke events recorded in 16 longitudinal datasets by Valtorta *et al*. (2015) revealed that loneliness and social isolation were associated with a 29% increased risk of CAD and a 32% increased risk of stroke, regardless of the gender[7]. The findings reflected the magnitude add on effects of loneliness and social isolation has on individuals' health, in addition of predisposing them to CAD. Accordingly, interventions targeting psychosocial risk factors for preventing CAD are warranted.

Key Topics under the Management of CAD

The holistic management of CAD should cover various aspects including diagnostic technologies, application of medications, surgical procedures, preventive measures, research on emerging therapies, interdisciplinary collaboration, long-term outcomes with follow-ups, as well as lifestyle modifications and cardiac rehabilitation (**Figure 2**)[8]. Among these, innovative diagnostic techniques for early detection and risk assessment, effective medications, and advanced surgical treatments are particularly crucial for improving the overall outcomes of CAD patients.

Cardiac computed tomography angiography (CCTA) is a non-invasive alternative to invasive coronary angiography (ICA) primarily used to evaluate coronary anatomy. CCTA allows rapid determination on the presence of coronary plaque and triage patients' that require further invasive evaluation and treatment, with high positive and negative predictive values[9].

Notably, patients with previous coronary artery bypass grafting (CABG) often require ICA, which is technically more challenging and incurs a higher risk of complications. In the BYPASS-CTCA trial (2023), undergoing CCTA before ICA was demonstrated to significantly reduce the procedure time of ICA and contrast-induced nephropathy, with improved patient satisfaction, compared to ICA alone. Furthermore, there was a significant reduction in incidence of 1-year major adverse cardiac events (MACE) in the CCTA+ICA group compared with the ICA group (**Figure 3**)[10].

Besides non-invasive imaging techniques, biomarkers have emerged as promising tools for early CAD diagnosis and risk assessment. A recent analysis of 3,072 CAD patients by Netto *et al*. (2022) suggested that plasma levels of troponin T, N-terminal pro B-type natriuretic peptide (NT-proBNP), copeptin, high-sensitivity C-reactive protein (hsCRP), and interleukin-6 (IL-6) showed a significant association with total mortality, whereas the levels of the biomarkers varied at different stages of CAD. Hence, incorporating the biomarker during diagnosis will likely enables fast and precise non-invasive identification of mortality risk in CAD patients, thus, allowing the tailoring of primary and secondary CAD prevention[11].

Personalised risk profiling encompasses genetic testing and risk assessment tools, which facilitates precision medicine in CAD management. Uncovering the genetic variants associated with the risk and treatment responses allows for tailored treatment strategies catering individual patient needs[8]. Interestingly, Zhou *et al*. (2024) recently developed a risk prediction model for recurrent cardiovascular (CV) events among Chinese patients. The model included a list of 125 risk variables, such as clinical laboratory tests and disease and medication history, which were used to help predict the risk of CV disease (CVD), of which 8 classes of CVD-related drugs were considered interactive covariates[12]. The risk prediction model is expected helpful in identifying individuals at high risk

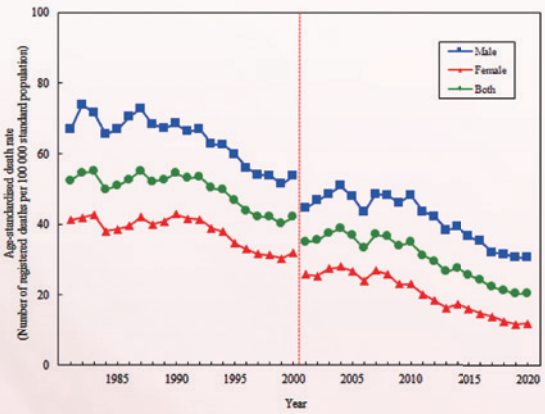


Figure 1. *Local age-standardised death rate of CAD by sex, 1981-2020*[1]

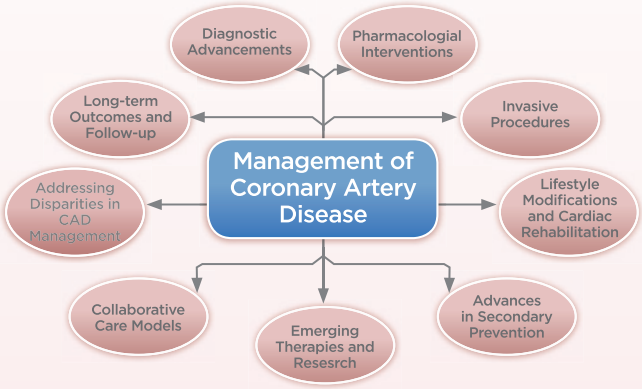


Figure 2. *Key issues in the management of CAD*[8]

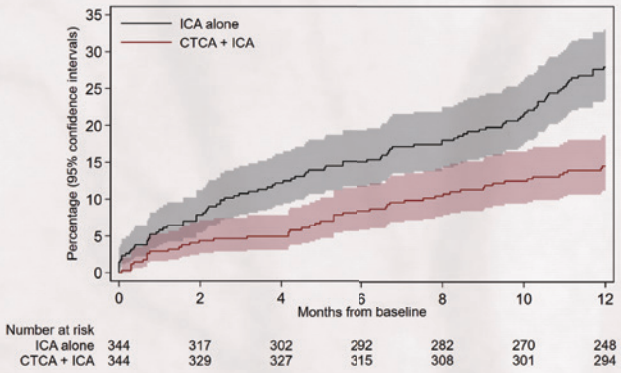


Figure 3. *MACE at 12 months in BYPASS-CTCA trial*[10]

of CAD, thereby enabling timely intervention and preventive measures.

The Cutting-edge Pharmaceuticals against CAD

The conventional medication treatment for stable CAD patients consists of beta blockers, calcium channel blockers, nitrates, angiotensin converting enzyme (ACE) inhibitors, and statins[8]. However, novel therapies for CAD have been emerging in recent years. Importantly, the use of a clopidogrel, a P2Y12 inhibitor, in patients with an acute coronary syndrome (ACS) is also well established.

In the HOST-EXAM Extended study (2023), clopidogrel monotherapy for long-term maintenance after percutaneous coronary intervention (PCI) was demonstrated to yield lower rates of a composite of all-cause death, non-fatal MI, stroke, re-admission attributable to ACS, and Bleeding Academic Research Consortium (BARC) type 3 or greater bleeding than aspirin after a median follow-up of 5.8 years[13].

Apart from P2Y12 inhibitors, maintaining a lower low-density lipoprotein cholesterol (LDL-C) is established to reduce the risk of atherosclerotic cardiovascular disease (ASCVD), and long-term maintenance of lower LDL-C is recommended by clinical guidelines for those at greatest risk of future ASCVD-related events[14]. In this regard, when statins are not tolerated or cannot be prescribed, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition was used to reduce the levels of LDL-C. For instance, the findings from the ORION-3 trial revealed that long-term treatment with inclisiran reduced LDL-C levels by 47.5% and the reduction was sustained over 4 years among patients at high CV risk (**Figure 4**)[15].

On the other hand, the 5-lipoxygenase (5-LO) pathway is responsible for the production of leukotrienes that have inflammatory and vasoactive actions and are involved in the innate immune response, whereas FLAP (5-lipoxygenase activating protein) is critical for the production of leukotrienes[16]. Hence, the inhibition of 5-LO or FLAP was hypothesised to reduce mortality, morbidity, and cardiovascular hospitalisation in patients with CAD by slowing the progression of atherosclerosis, to enhance coronary microvascular function, and to improve ventricular contractility following MI[17]. In the phase 2a FLAVOUR trial, AZD5718, a FLAP inhibitor, was demonstrated to reduce leukotriene biosynthesis in patients with recent MI and was well-tolerated[18].

While new medications against CAD are slowly emerging, recently, the focus on primary and secondary prevention of CAD has shifted towards optimising the patient treatment outcomes, for instance, the use of single antiplatelet therapy (SAPT) reducing CAD risk.

Life-saving Innovative Surgical Treatments

From the initial application in improving visualisation with enhanced endoscopic camera control to the recent robotic surgical systems which permit the manipulation of surgical instrument through limited thoracic incisions, robot-assisted technology has revolutionised surgical procedures in cardiology.

A retrospective analysis by Lin *et al*. (2021) compared the outcomes of conventional coronary-artery bypass grafting (C-CABG) and robot-assisted CABG (R-CABG) using the Da Vinci robotic operation system in patients with multi-vessel CAD (n=516) suggested that in-hospital and long-term mortalities were lower in the R-CABG group. However, the incidences of target lesion revascularisation (TLR), target vessel revascularisation (TVR), MI, and stroke were not significantly different between the two groups. The study thus concluded that R-CABG could be an effective alternative to C-CABG for multi-vessel CAD patients with fewer clinical complexities in real-world practice[19].

In addition to enhancing precision, robot-assisted technology also allows tele-operation. The clinical operation of tele-stenting was illustrated in the REMOTE-PCI study (2017). During the operation, a physician operator performed stenting on a patient in a separate physical location using a combination of robotics and telecommunications. Among the 20 participating patients, procedural success, i.e. <30% residual stenosis upon completion of the surgery in the absence of death or repeat revascularisation before discharge, was achieved in 19 (95.0%) patients[20].

The robot-assisted surgical procedures not only benefitted patients for improving treatment outcomes and minimising the risk of complications, but it also lowered the burden for frontline physicians by reducing exposure to occupational radiation and orthopaedics hazards[17].

Besides the advancement in surgical procedures, innovation in treatment instruments is also remarkable. Drug-coated balloons (DCB), designed to administer anti-proliferative agents to coronary lesions without the use of a metallic stent, have emerged as a potential alternative to drug-eluting stent

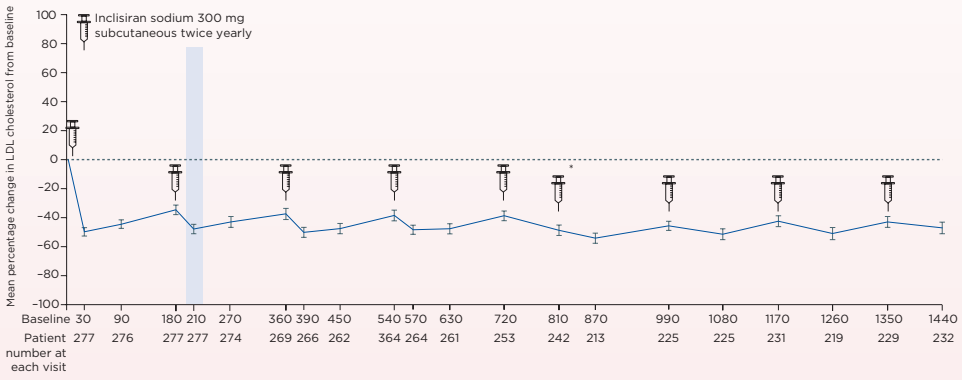


Figure 4. *Mean percentage change in LDL-C from baseline to day 1440 (4 years) yielded by inclisiran*[15]

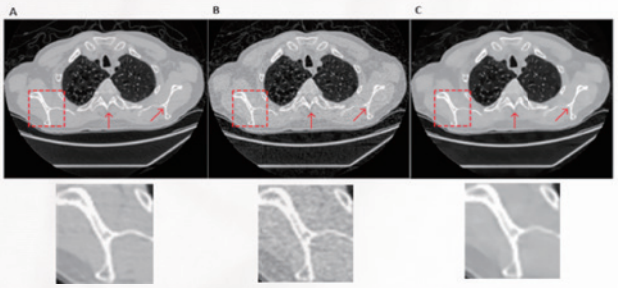


Figure 5. *Restoring chest CT image with the specific zoomed regions within the red box[23], A) normal dose image, B) low-dose image, C) CNN-processed image*

(DES), combining the advantage of local drug release during balloon angioplasty without the long-term disadvantage of DES, including impaired vessel motility and increased risk of late thrombosis[21].

A recent randomised control trial (RCT) involving 600 patients with in-stent re-stenosis undergoing percutaneous coronary intervention (PCI) by Yeh *et al*. (2024), target lesion failure was significantly lower in the paclitaxel-coated balloon group (17.9%) compared with the uncoated balloon group (28.6%, p=0.003). Also, ischemia-driven TLR and target vessel MI were also lower after treatment with a paclitaxel-coated balloon[22]. The results thus highlighted that DCB was superior to an uncoated balloon with respect to the composite end point of target lesion failure and was an effective treatment option for patients with coronary in-stent restenosis.

The Advancements in the Era of Artificial Intelligence

The rapid progress of artificial intelligence (AI) has created new opportunities to improve the interventional workflow in managing CAD. While image acquisition is crucial for guiding coronary intervention, AI has been applied to improve imaging quality while reducing artifacts and the radiation dose. For example, convolutional neural networks (CNN) architecture has been applied for restoring images from low-dose computed tomography (CT) images (**Figure 5A-5C**)[23].

In view of diagnosis and risk stratification, deep learning (DL) models have proven excellent performance in the diagnosis of stenosis using dedicated CNN architectures. Interestingly, Du *et al*. (2021) trained a DL model based on a dataset of 20,612 angiograms, in which 13,373 angiograms were labelled with coronary artery segments, and 7,239 were labelled with special lesion morphology. The DL model was reported to predict coronary artery segments with an accuracy of 98.4%, and the recognition sensitivity was 85.2%. Importantly, the model took only 2 seconds for the automatic recognition[24]. With the exceptional diagnostic performance, the DL architecture provides a coronary diagnostic map and is expected to help cardiologists to flag and diagnose lesion severity and morphology during the intervention.

Given that intravascular imaging post-stenting is indicated to evaluate the result after stent deployment, some DL models have been developed for rapid and automatic quantification of stent expansion and apposition. Yang *et al*. (2021) developed a DL method to automatically analyse stents with both thin (≤0.3mm) and very thick tissue coverage (>0.3mm), and an algorithm to accurately analyse stent area for vessels with multiple stents. Three-fold cross-validation demonstrated that the algorithm achieved a precision of 0.932 and a sensitivity of 0.939 for stents with thin tissue coverage, and a precision of 0.856 and a sensitivity of 0.874 for stents with very thick tissue coverage (**Figure 6A-6C**)[25]. Based on the results, the method can facilitate the evaluation of stent implantation and post-stent tissue coverage.

Although there are still limitations of DL and unaddressed challenges ahead, advanced DL algorithms open new opportunities for precise diagnosis and tailored treatment in cardiology with a high degree of automation, reduced radiation, and enhanced risk stratification. Vitally, the technology is expected to benefit patients by optimising treatment outcomes.

Shaping the Future of CAD Management

The recent advancements in diagnostic methods and therapies have significantly reduce the burden of CAD. Our better understanding on the pathophysiology of the disease facilitates the development of effective medications and personalised treatment, whereas the use of AI not only enhance the efficiency in clinical operation, but also help physicians overcome technical difficulties during surgical treatments. While the innovations undoubtedly have revolutionised the landscape of clinical management of CAD, the role of education on healthy lifestyle remains crucial. Prevention is always the most important yet is most often overlooked. Therefore, clinicians should empower their patients to take control of their health and manage their disease holistically.

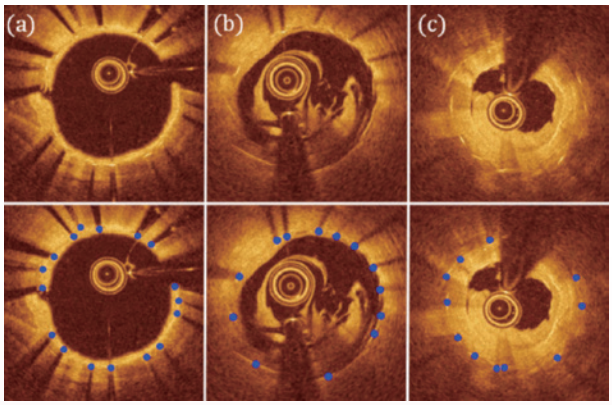


Figure 6. *Stent detection results by the proposed algorithm: the top row shows original images and the bottom row illustrates the corresponding detected stent struts[25], A) clear lumen with thin-medium tissue coverage, B) significant residual luminal blood, C) thrombus and very thick tissue coverage*

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Self Study Questions (1 CME point):

1. Which of the following about the meta-analysis by Valtorta et al. (2015) is/are correct?

i. The study included only CAD events

ii. The results reflected no gender difference

iii. Loneliness and social isolation were associated with the increased risk of CAD and stroke

A) i only

B) i and ii

C) ii and iii

D) All of above

2. Which of the following is/are the reported outcomes of undergoing CCTA before ICA demonstrated in the BYPASS-CTCA trial?

i. Reduction in the procedure time of ICA compared with ICA only group

ii. Reduction in the incidence of 1-year MACE compared with ICA only group

iii. Reduction in direct medical expenses compared with ICA only group

A) i only

B) i and ii

C) ii and iii

D) All of above

3. Which of the following statement about the clinical trials of cutting-edge pharmaceuticals against CAD is incorrect?

A) The HOST-EXAM Extended study showed that clopidogrel monotherapy for maintenance after PCI yielded lower rates of a composite of all-cause death, non-fatal MI, stroke, re-admission attributable to ACS, and BARC type 3 or greater bleeding.

B) The median follow-up period in the HOST-EXAM Extended study was 4 years.

C) The ORION-3 trial showed that inclisiran reduced LDL-C levels and the reduction was sustained over 4 years among patients at high CV risk.

D) The FLAVOUR trial, AZD5718 was demonstrated to reduce leukotriene biosynthesis in patients with recent MI and was well-tolerated.

4. Which of the following statements is correct?

A) According to Lin et al. (2021), R-CABG yielded lower incidences of TLR, TVR, MI, and stroke as compared to C-CABG.

B) In the REMOTE-PCI study, procedural success was achieved in 90.0% patients.

C) The long-term disadvantages of DES include impaired vessel motility, and increased risk of late thrombosis.

D) In the RCT by Yeh *et al*., target lesion failure occurred in 28.6% of patients in the paclitaxel-coated balloon group.

5. Which of the following about the study by Du et al. (2021) is/are correct?

i. The DL model was trained based on a dataset of 13,373 angiograms labelled with coronary artery segments and 7,239 angiograms labelled with special lesion morphology

ii. The DL model was reported to predict coronary artery segments with an accuracy of 85.2%, and the recognition sensitivity was 98.4%

iii. The model took only 2 seconds for the automatic recognition.

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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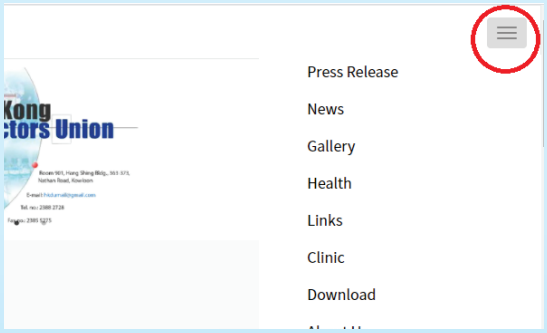

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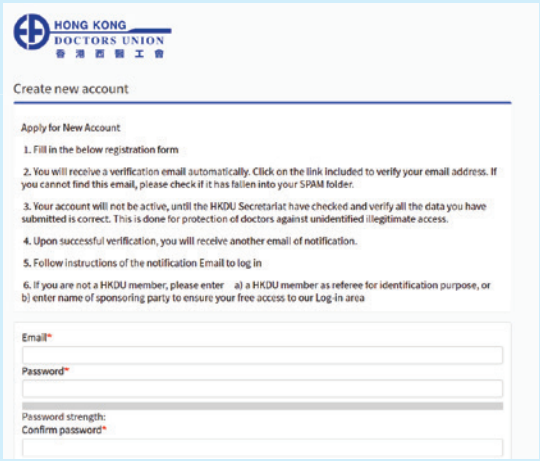


5 經本會秘書處核實後，登入資料將傳送至閣下指定的電郵信箱。利用登入資料，不論何時何地，閣下都可以得到本會所提供的醫療資訊。

by Dr. Mohsin Roshan

The Unmet Needs in Relapse/ Refractory Multiple Myeloma: A Clinical Challenge

Dr. Justin Li

Specialist in Haematology, Tuen Mun Hospital

Multiple myeloma (MM) is a haematologic malignancy characterised by abnormal clonal plasma cells in the bone marrow with a potential for uncontrolled growth causing destruction, osseous lesion, acute kidney injury (AKI), anaemia, and hypercalcaemia. The median age of onset for MM is 69 years, and approximately 63% of patients diagnosed with MM are above the age of 65[1]. MM accounts for 176,404 new cases and 1.2% of cancer-related deaths globally[2]. Bony destruction seen in MM is a result of an increase in osteoclast formation with no bony repair in response to previous bone destruction[3]. Approximately 1-2% of patients exhibit extramedullary disease (EMD) at the time of the initial diagnosis, and 8% may develop EMD at later stages of the disease[4]. Relapsed or refractory MM (RRMM) constitutes as an unmet medical need in patients with MM since most of them have a median survival range from 6 to 9 months with remission period becoming shorter after each relapse[5,6]. Therefore, to address the challenging nature of the RRMM, we have invited Dr. Justin Li, a haematology specialist, to highlight the outstanding issues with RRMM through a case-based sharing and discuss the novel therapeutic options available for patients with RRMM.

An Unusual Case of RRMM

Thalidomide was the first immunomodulatory drug (IMiDs) introduced to treat MM due to its potential anti-angiogenic activity[7]. The early success of thalidomide prompted an investigation into additional IMiDs, the most notable of which are the Lenalidomide and Pomalidomide[8]. Dr. Li explained, while cure remains an ultimate goal, converting myeloma into a chronic disease through the sequencing of available therapies, guided by disease biology appears to be within the grasp[9]. On this note, Dr. Li shared a clinical case of a 79-year-old retired healthcare worker who presented with a two-year history of chest and lower back pain which has worsened since the July 2020. A left-sided supraclavicular mass with apical shadow was seen on the chest x-ray, therefore, the patient underwent a CT thorax to exclude lung carcinoma. The CT reported an extrapulmonary mass with left 1st medial rib bony destruction but no lung parenchymal involvement (**Figure 1**); in addition, there were lytic lesions involving the 10th thoracic vertebra (T10). Therefore, to assess further, a diagnostic biopsy was offered which the patient declined, according to Dr. Li. Further blood tests showed a haemoglobin (Hb) of 9.2g/dL, with normal serum calcium but mildly deranged serum creatinine (130μmol/L).

The serum protein electrophoresis (SPEP) was 42g/dL, mainly involving IgA lambda (λ) and marrow analysis showed around 41% of plasma cells, consistent with a diagnosis of plasma cell myeloma. The fluorescence in-situ hybridisation (FISH) demonstrated chromosome 1 gain (+1q) as per Dr. Li and according to studies, +1q gain is the most common cytogenetic abnormality seen in 20-50% of newly diagnosed cases of MM[10]. In this case, the patient was eventually diagnosed with the Revised International Staging System (R-ISS) II and underwent a positron emission tomography-computed tomography

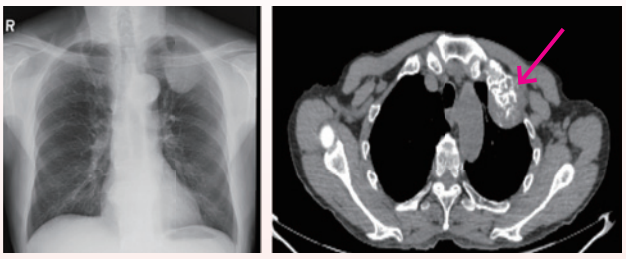
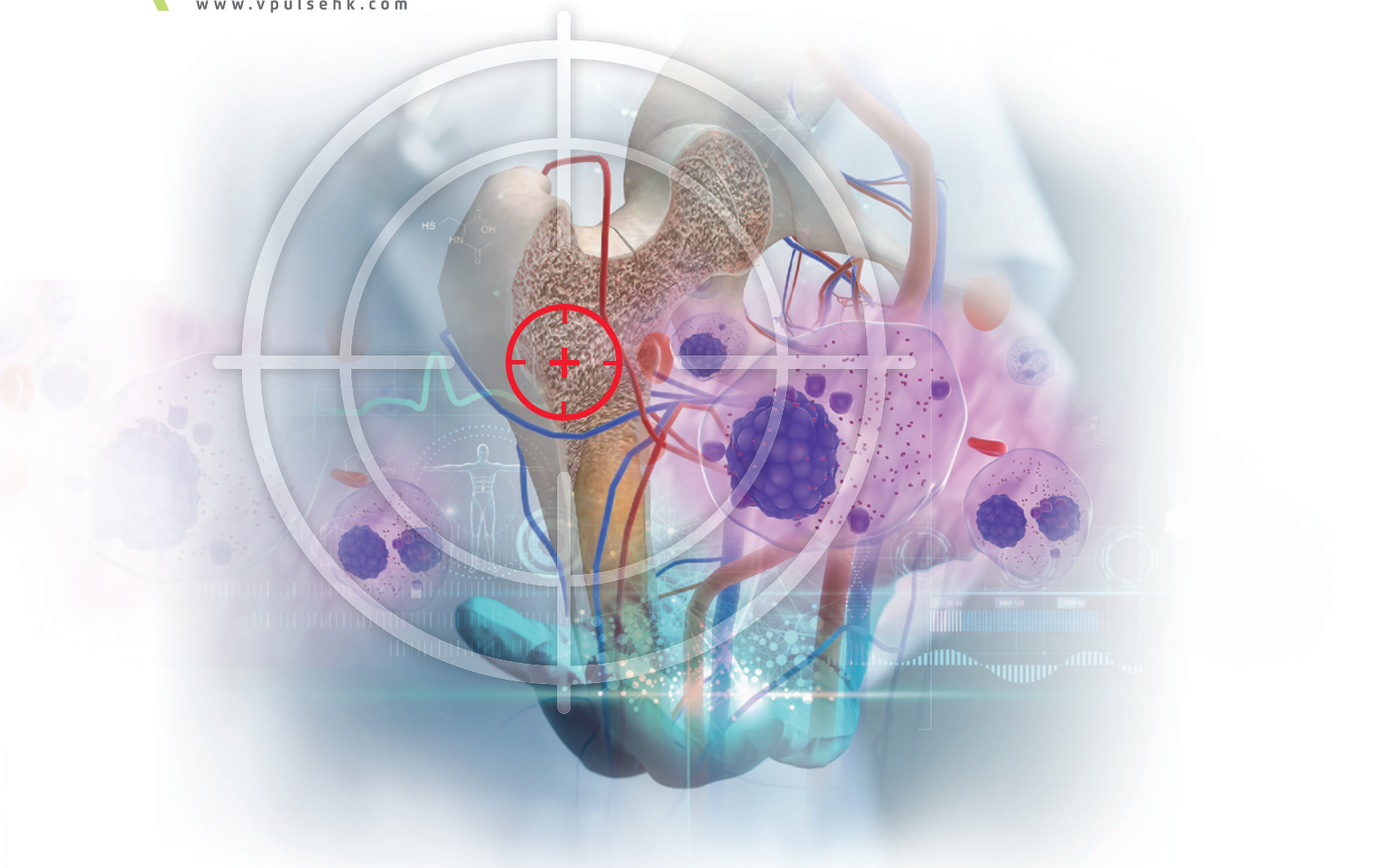


Figure 1. Chest x-ray and CT revealed extrapulmonary mass on the 1st left rib (red arrow) with lung parachymal sparing.



(PET-CT). The PET-CT findings were consistent with the previous CT thorax showing a left 1st rib bony lesion with T10 lytic lesion, in addition to vertebrae collapse at T10 and 3rd lumbar (L3) levels. The patient was eventually initiated onto bortezomib/thalidomide/dexamethasone (VTd) treatment in early October 2020 and had around 8 treatment cycles of VTd until the April 2021. According to Dr. Li, "the patient responded well to the VTd treatment as his SPEP levels dropped from 42g to 2g (**Figure 2**)." Therefore, bortezomib was offered as a maintenance treatment since there was a high-risk of recurrence, but the patient refused. Instead, he opted for the oral treatment and was commenced onto thalidomide 50 mg (nocte).

During the follow-up, PET-CT was repeated, and new bony lesions were reported. Thus, dexamethasone 20 mg weekly was added to the treatment regimen. The patient reported worsening bone pain in June 2021 after having only 1 treatment cycle, and repeated tests showed uptrending SPEP levels (up to 9g). A further bone marrow aspirate was obtained in September 2021 due to worsening of symptoms and it showed 22% of clonal bone marrow plasma cells, once again consistent with the diagnosis of plasma cell myeloma.

Hence, the patient was commenced onto ixazomib-based therapy for approximately 5 treatment cycles prior to reporting intolerable generalised rash (**Figure 3**). Therefore, the treatment was escalated to pomalidomide/dexamethasone (Pom/Dex) and no further rashes were reported. Dr. Li elaborated that the patient was readmitted on two different occasions after being discharged and on his last admission, he presented with persistent headaches. Dr. Li emphasised that the blood cultures revealed disseminated cryptococcal infection even though the patient was not neutropenic. Thus, antifungals (flucytosine and ambisome) were commenced for approximately 4 weeks followed by fluconazole 400 mg for 8 weeks. His MM treatment was temporarily discontinued for three months to allow the underlying disseminated fungal infection to be treated.

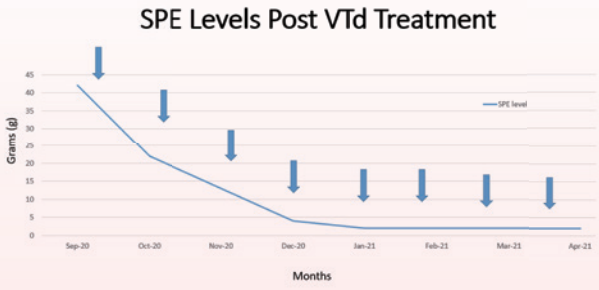


Figure 2. SPE levels post VTd treatment dropped from 42g to 2g. SPE= serum protein electrophoresis, VTd= bortezomib, thalidomide, dexamethasone.

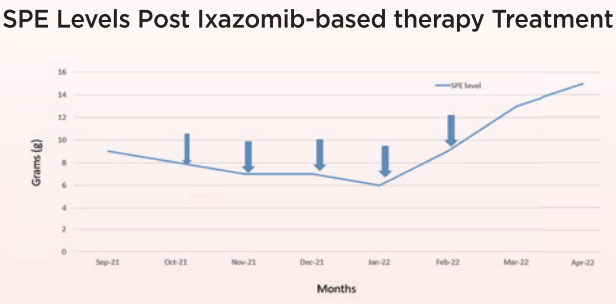


Figure 3. SPE levels post Ixazomib-based therapy treatment showing an increase in SPE levels after 4th treatment cycle. SPE= serum protein electrophoresis.

To date, the patient remained on maintenance dose of fluconazole 200 mg, nevertheless, repeated tests showed the SPEP levels were rising (up to 7g) shortly after the discontinuation of the Pom/Dex treatment. Therefore, the Pom/Dex treatment was recommenced. After completing 13 treatment cycles of Pom/Dex, the SPEP levels eventually decreased and remained low (**Figure 4**). Dr. Li explained that the patient is due his 14th dose in August 2023 and so far, he has been responding very well to the Pom/Dex treatment with no major haematological toxicity.

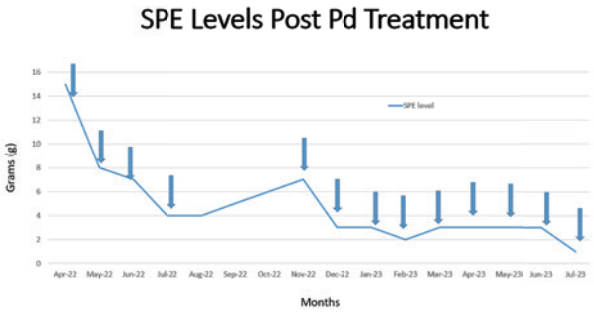


Figure 4. *SPE levels post Pd treatment showing a decline in SPE level at 13th cycle. SPE= serum protein electrophoresis, Pd= pomalidomide, dexamethasone (Pom/Dex)*

Clinical Trials to Real-World Effectiveness of Pom/Dex in RRMM:

Even though the therapeutic options for RRMM are increasing, the treatment efficacy for RRMM remains a critical challenge. As the latest IMiD, pomalidomide has shown to be more potent, yet less toxic than thalidomide and lenalidomide[11]. This was demonstrated in a multi-centred, retrospective registry-based study which reviewed the medical records of 49 consecutive patients who have undergone Pox/Dex treatment for RRMM. The results showed that the overall response rate (ORR) of Pom/Dex was 47.7% with a median progression-free survival (PFS) of 4 months in a real-world setting[11]. In addition, patients who received two prior lines of treatment had a higher ORR compared to those who received more than two prior lines of treatment (55.2% vs 33.3%; p= 0.045). The study concluded that the primary lenalidomide refractoriness reduced the risk of myeloma progression following Pom/Dex treatment (hazard ratio, 0.14; p= 0.001)[11]. These findings were also substantiated in a Czech study that analysed the data of patients with RRMM from nine centres between 2013 and 2018. The results showed patients treated with Pom/Dex had ORR of 51.8% with the clinical benefit rate of 67.1%. Furthermore, the median PFS was 8.9 months, and the medial overall survival (OS) was 14.2 months in patients treated with Pom/Dex. These results further elaborated the findings that the efficacy of Pox/Dex in a real-world setting is comparable to that of the clinical trials[12].

Notably, recent studies have shown that a longer duration of therapy utilising the maintenance treatment strategy being more beneficial in improving the patient outcomes. Moreover, the disease refractory to the novel agents such as the IMiDs and proteasome inhibitors is being encountered more frequently and earlier in myeloma patients[13]. Therefore, a longer duration of treatment may correlate to a higher response rate according to Ailawadhi *et al*., (2018) who conducted a large, multi-cohort clinical trial testing various doses and treatment schedules of Pox/Dex in patients with RRMM[13]. In this trial, 345 patients were divided into six cohort groups based on the dose (2 mg or 4 mg daily) and types of prior lines of therapies (lenalidomide or lenalidomide and bortezomib or <3 prior regimens) taken. A response rate of 35% was reported in all cohorts with a higher response rate seen in cohorts with a fewer prior lines of therapy[13]. The longest PFS and OS in any cohort were 13.1 and 47.9 months, respectively[13]. The results obtained from the clinical trial justified the longer duration of Pom/Dex used in the case presented by Dr. Li. In this regards, Dr. Li suggested that patients with MM often require more than first line treatment, and Pox/Dex should be one of the key arsenals when treating RRMM. In conclusion, continuing therapy from the first relapse to the disease progression may have the potential to suppress the residual disease, thereby, may extend the overall survival; this represents the paradigm shift allowing MM to be managed as a chronic illness[14].

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by Jasmine Lai

Is Gene Therapy or Bioartificial Organs the Future of Medical Treatment?

Rare diseases typically have a prevalence below 0.05% and constitute around 10,000 diseases, cumulatively affecting over 5% of the global population. Although there is a large unmet need in treatment, the recent advent of gene therapy is beginning to close the gap[1]. On the other hand, a report in 2017 by the Global Observatory on Donation and Transplantation with data representing approximately 75% of the global population showed that the 139,024 organ transplantations performed that year barely accommodated 10% of the global need[2]. High hopes are on bioartificial organs to reduce the severity of this unmet need. Both fields of therapy represent a new era of biotechnology, but their role in the future of medical treatment does not solely depend on innovation alone.

Gene Therapy and Its Current Treatment Landscape

The United States (U.S.) Food and Drug Administration (FDA) defines gene therapy as a technique that modifies a person's genes to treat or cure disease. Today, gene therapy is delivered through various modalities, such as vectors, chimeric antigen receptor T cell immunotherapy, and now genome editing technology[3]. These are often used to target rare diseases, but their high price tag challenges their longevity in the market. However, lessons gradually gathered in the past decade have paved the way for improved treatment options for patients currently facing limited options[4].

Viral Vectors to Treat Inherited Retinal Dystrophy

A successful case of a gene therapy technique involves in vivo DNA insertion using adeno-associated virus (AAV) vectors in Leber's Congenital Amaurosis type 2 (LCA2), a type of inherited retinal dystrophy (IRD) that was previously incurable and untreatable. IRDs are often caused by a defective gene copy, and through gene supplementation, a functional copy of the gene can be delivered to the target tissue using engineering viruses as vector delivery systems. Patients with LCA2 are blind at birth or in early childhood due to mutations in the gene coding for retinal pigment epithelium-specific 65-kilo-dalton protein (RPE65) that often results in impaired 11-cis-retinal regeneration in the visual cycle and non-functional photoreceptors.

Voretigene neparvovec (VN) is an AAV-based, recombinant, non-integrating vector gene therapy that is administered via subretinal injection with a gap of 6–18 days between each eye[1]. Results from the randomised, controlled, open-label, phase 3 trial showed that patients treated with VN demonstrated a strong and durable improvement in visual acuity 1 year after treatment, as well as improvements in visual field and light perception[5]. Moreover, results from the ongoing, 2 year, prospective PERCEIVE study was published this year with the outcomes of 103 patients treated with VN. The findings were consistent with the VN pivotal trials, but sustained improvements in full-field light-sensitivity threshold appeared better in patients aged <18 years than adult patients (**Figure 1**), highlighting the advantages of early treatment[6].

The Acceptance of Ocular Gene Therapies and the Importance of Social Inclusion

Despite being a relatively new treatment modality, the response to using gene therapies for orphan diseases has been positive overall. The United Kingdom National Institute for Health and Care Excellence (NICE) supports the provision of VN, explaining that although patients would remain visually impaired, the high unmet need in patients with RPE65-mediated IRDs can benefit from VN for preventing further deterioration in vision[7]. Meanwhile, in an international cross-sectional survey conducted among potential recipients with IRDs, 90% of participants indicated that they would likely consider gene therapy if it was available, and over 75% of participants would consider travelling to another country to access it[8].

However, even somatic gene therapies are laced with bioethical and societal implications. It is important to consider that blindness is a disability, and is not considered a life-threatening condition. A qualitative study that characterised the attitudes of people with IRDs revealed that despite the general support over genetic editing, participants had concerns over retaining personal choice, accessibility, and social inclusion[9].

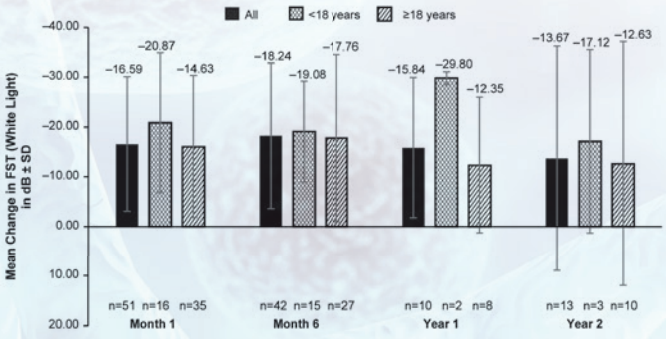

Figure 1. Mean change from baseline in FST (white light) up to 2 years after VN administration in all patients, patients aged <18 years and those aged ≥18 years. dB, decibel; FST, full-field light-sensitivity threshold testing; n, number of eyes; VN, voretigene neparvovec. Baseline data were available for 127 eyes. Error bars represent the standard deviation[6].

CRISPR Comes of Age with Sickle Cell Disease

While AAV vectors are limited to somatic post-mitotic cells and short DNA segments, genome editing technologies are more versatile and have immense potential in possible applications and treatments[1,10]. Exagamglogene autotemcel (EA) is the first gene therapy approved by the FDA that utilises clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 (CRISPR/Cas9) techniques, and is indicated for transfusion-dependent β-thalassemia and as treatment for sickle cell disease in patients aged ≥12[11]. In these

debilitating, hereditary, and chronic conditions, gene mutations affect haemoglobin production and function resulting in haemolytic anaemia, meaning that patients require repeated blood transfusions as frequent as once or twice a month[11].

EA is a one-time, haematopoietic stem cell transplant (HSCT) where the patient's own CD34+ cells with an erythroid lineage are modified to reduce b-cell lymphoma/leukaemia 11A (BCL11A) expression, thereby, allowing an increase in fetal haemoglobin production that has a higher affinity for oxygen compared to adult haemoglobin[12]. These findings were substantiated in a phase 3 clinical trial, where out of 28 patients, 89% achieved maintained a weighted average hemoglobin (Hb) ≥9 g/dL without requiring further red blood cell transfusions for over 6 and 12 months, with clinical significant improvements in quality of life[13].

The Challenging Survival and Long-term Outlook of Gene Therapy

Even though β-thalassemia (major) and sickle cell disease are the most prevalent rare diseases, many patients are precluded from HSCT and gene therapies since the majority of newborns with the conditions live in developing countries and may never have access to such treatments[14]. Additionally, betibeglogene autotemcel (BA) is a lentiviral vector, stem cell-based gene therapy that was previously approved in Europe in 2019 for patients with β-thalassemia requiring regular blood transfusions. However, disagreements in the payment model led to the manufacturers withdrawing from the European market. In the United States (approved in 2022), manufacturers agreed to refund 80% of the costs to patients who fail to maintain transfusion independence up to two years later[4]. Newer flexible reimbursement models for gene therapies are in development, to ensure that treatments are accessible for patients.

Other techniques that build on CRISPR or that have reimagined it entirely are expanding the precision and number of targets of genome editing. For instance, whereas CRISPR/Cas9 systems can only make cuts, a newly discovered technique, known as bridge ribonucleic acids (RNAs), may enable larger-scale genome design that unifies insertion, excision and inversion (**Figure 2**)[15]. However, when discussing the limitations of single-treatment gene therapy, Baylot *et al*. (2024) noted the potential risk of irreversibility if adverse events occurred and suggested to include on and off switches to prevent overexpression of deoxyribonucleic acid breaks[16].

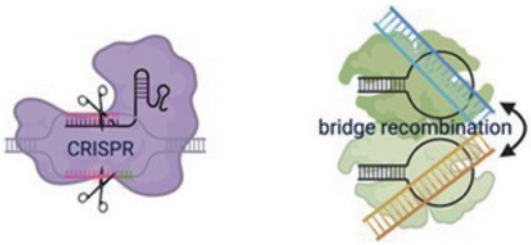

Figure 2. *A simplified schematic of the mechanism in CRISPR and Bridge RNA[17].*

Bioartificial Organs for Transplants and Its Current Treatment Landscape

Bioartificial organs are conceptually structures made of biologically based materials that may functionally be analogous to natural organs, and are still being developed in pre-clinical research settings[18,19]. The significant growth in research on newer techniques has allowed further exploration of bioartificial organs as the ultimate avenue of hope to overcome the issues of tissue rejection, organ shortage and poor-quality donor organs found with conventional donor organ transplantation.

Lessons Learned from Scaffolding the Bladder

The concept of developing a bioartificial organ originates from advances in tissue engineering and regenerative medicine. In 1999, Atala *et al*. (2006) successfully engineered an autologous bladder in seven patients aged between 4-19 with spina bifida whom did not require a complete bladder substitution. Urothelial and muscle cells were extracted from patients, cultured and seeded onto a biodegradable bladder-shaped scaffold made of collagen before being reconstructed and implanted into patients. After an intensive follow-up for an average of 46 months, they found that the bladder retained an adequate structural architecture and phenotype. Moreover, bowel function returned promptly after surgery with no subsequent metabolic consequences or urinary calculi, with normal mucus production and renal function[20]. This was an important stepping-stone in the field as the researchers identified the need for a scaffold to support cells to organise themselves into 3-dimensional structures (**Figure 3**)[21].

The Steps between Bio-tissue and Bio-organ

Natural, decellularised scaffolds may have better outcomes than synthetic biomaterials as they retain proteins, extracellular

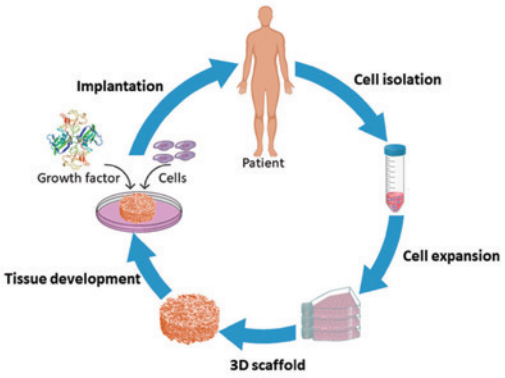

Figure 3. *Schematic of scaffold-based tissue engineering*[22].

matrix components , and chemical and biological cues similar to the native tissue making them more compatible with the target cells[23]. However, the field of reconstructive urology is still challenged by the concept of replacing the entire bladder, notwithstanding to other organ systems.

Other than cellular growth, differentiation, maturation, and scaffolding, bioartificial organs should have adequate mechanical, chemical and structural properties. With the bladder, repeated coordinated bladder contractions and relaxation allows for filling, storing and emptying. And as a hollow, fluid-containing organ, sufficient structural integrity is required to avoid collapse or leakage. But as of now, replacing bladder function by using a colon conduit (i.e. an ileal conduit or neobladder generation) still remains the gold standard treatment such as in bladder cancer patients requiring a radical cystectomy, despite of a number of complications that may arise postoperatively[23].

The Regenerative Capabilities of the Liver

Solid organs are complex owing to its cell density, high oxygen requirements and multifunctionality. The liver is likely to be the first bioartificial solid organ to be developed since it has the capacity to self-regenerate and recover from disease or injury. Moreover, hepatocytes can already be engineered from induced pluripotent stem cells that are derived from normal somatic adult cells and are potentially limitless in supply[19].

The potential of a bioartificial liver device has been initially tested in patients with extended liver resection. Considering that a large portion of the liver is removed, patients are at greater risk of post-hepatectomy liver failure[24]. Facilitated liver regeneration to support the remnant liver in these patients may provide, and insights before whole organ engineering occurs Wang *et al*. (2023) conducted a single-arm open-label clinical study on a bioartificial liver in seven patients with extended liver resection. The team produced hepatocytes by inducing human pluripotent stem cells, dedifferentiating hepatocytes or transdifferentiating human fibroblast, and created bioartificial liver supporting systems composed of extracorporeal bioreactors filled with hepatocytes. The initial results revealed that the liver was well-tolerated and associated with improved liver function and liver regeneration (**Figure 4**), meeting the primary outcome of the incidence of adverse events, including safety and tolerability up to 3 months after therapy[24].

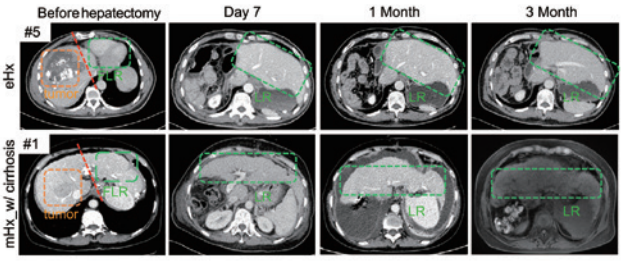

Figure 4. *Assessment of liver regeneration in patients with extended liver resection by CT volumetry. The yellow box represents the tumor, and the green boxes represent the future liver remnant or liver remnant*[24].

Immunosuppression and the Complexity of Sourcing

An important consideration of bioartificial organ development are ethical and safety issues of different cell sources which were systematic review by de Jongh *et al*. (2022)[19]. For instance, allogenic cells can be used indefinitely, but unlike consenting to an organ donation, donors have less insight and control over how the cells are used. Xenogeneic cells or tissues carries a risk of zoonoses and face additional socio-cultural barriers. Moreover, when genetically modified cells are used to produce entire organs, the risks of tumour formation or epigenetic changes is exponential. Coupled with the need for immunosuppression, the authors advise on the minimal use of xenogeneic and genetically modified sources[19]. But if the goal is immunosuppression-free transplantation (**figure 5**)[25] to reduce the chance of immune rejection and the dependability on immunosuppressives post-transplantation, the significant structural hurdles of harvesting and storing autologous cell sources must be overcome[19].

To conclude, the immense pace at which gene therapy has progressed from bench to bedside or the collaboration of technologies in bioartificial organs bring immense hope for the future. But with both forms of therapy, succinct basic research must be supported by patient involvement while considering their broader implications.

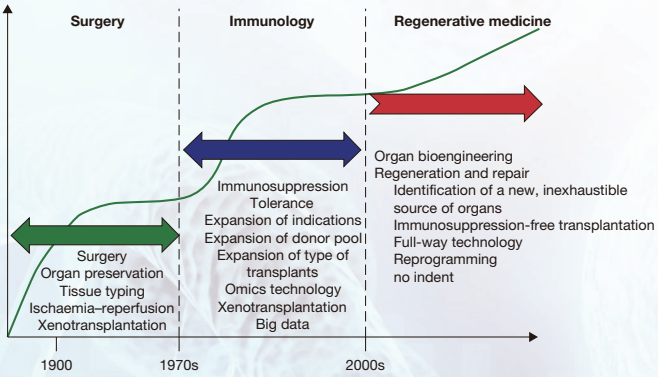

Figure 5. *Phases in the history of organ transplantation*[25].

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LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

EFFACLAR H ISO-BIOME

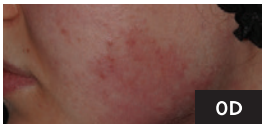
ADJUNCTIVE THERAPY FOR ACNE TREATMENTS

TESTED ON PATIENTS UNDER ACNE TREATMENTS

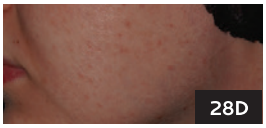
COMPENSATING DRYING EFFECTS OF TREATMENTS.

SOOTHING AND REPAIRING THE SKIN BARRIER.

AFTER 28 DAYS OF **EFFACLAR H** ISO-BIOME ROUTINE WITH EPIDUO 0.1, SKIN SENSITIVITY IS SIGNIFICANTLY REDUCED



AFTER FAILURE TO MANAGE SKIN SENSITIVITY UNDER EPIDUO 0.1 FOR MORE THAN 1 MONTH



AFTER DAILY USE OF **EFFACLAR** H ISO-BIOME ROUTINE WITH EPIDUO 0.1

Protocol: Mean score, clinical study with 43 subjects

Hypo-Allergenic Formula
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by Dr. Mohsin Roshan

Breaking Through the Treatment-Resistant Depression with Esketamine

Dr Marco Marchionni, MD

MRCPsych (UK),
National Health Service (NHS),
United Kingdom (UK)

Major depressive disorder (MDD) is highly prevalent and affects more than 264 million individuals, globally. Remarkably, despite treatment, up to half of the patients with depression fail to reach remission and are at risk of experiencing treatment-resistant depression (TRD). The diagnosis and treatment of TRD can often be challenging due to co-existence of other mental disorder and increased treatment resistance. Traditionally, TRD patients non-responsive to pharmacotherapy had been treated with the electroconvulsive therapy (ECT). However, recent studies have highlighted a potential role of ketamine, and esketamine as a potential treatment for patients with TRD. Therefore, we have invited Dr. Marco Marchionni, from the NHS to discuss the change in TRD treatment paradigm.

Depression: The New Invisible Plague

MDD is highly prevalent and associated with substantial burden and economic costs. Notably, more than 264 million adults live with depression, globally and nearly half of all cases are from the Asia-Pacific region[1]. Interestingly, the World Health Organisation (WHO) has suggested MDD as the single largest contributor for loss of healthy life[2]. Furthermore, despite available treatment, up to half of the patients with depression fail to reach remission, as a result their risk of experiencing TRD increase[1]. What is TRD? Dr. Marchionni explained that TRD is defined as a lack of clinically meaningful improvement after treatment with at least 2 different antidepressants at adequate dosage and duration in the current depressive episode. Approximately, 30% of MDD patients suffers from TRD and even patients without TRD that initially responded to antidepressants may experience worsening of symptoms since the time required to reach the full effectiveness of an antidepressant is around 4-7 weeks[3].

Hence, patient suffering from TRD often have a higher healthcare utilisation and the need for a higher intensity treatment. In addition, the higher indirect costs reported in TRD patients is a consequence of relatively greater impairment in physiological, higher workplace disability and absenteeism. Dr. Marchionni emphasised that patients with TRD also have a disproportionately higher rates of suicide compared to the general population. In fact, studies have consistently found that patients with TRD have 29%-39% higher risk of all-cause mortality compared with those without TRD. These are further plagued by co-existence of other mental health problems in these patients since 45%-67% of patients with depression also have comorbid psychosis or anxiety disorder; thereby, predisposing them to lower remission rates. Thus, the unmet treatment needs persist in TRD patients and a novel therapeutic approach is urgently required to provide rapid symptomatic relief and support for these patients[2].

Dampening the Siege of TRD

TRD is often difficult to diagnose due to pseudo-resistance. What is pseudo-resistance? Dr. Marchionni stressed that pseudo-resistance is when patients with depression are prescribed with suboptimal doses of an antidepressant or had early discontinuation of a medication due to intolerable side effects, patient non-adherence, or under-dosing. Furthermore, the clinical picture can be complicated further by co-existence of other mental health disorders[4]. Are there any diagnostic tools that may help when diagnosing patients with TRD? Yes, there are, as per Dr. Marchionni as he explained that prospectively using objective clinical scales such as the Hamilton Depression Rating Scale (HDRS) and the Inventory of Depressive Symptomatology is often helpful. Other tools such as the Antidepressant Treatment History Form-short form (ATHF-SF) can be useful in delineating the nature and course of treatment resistance[4]. Considering the complexity of the condition, how are TRD patients treated? Patients with TRD have traditionally been treated with augmentation or adjunctive therapies which includes the addition of a second medication not usually considered as an antidepressant on its own, to a first-line treatment[4].

If these are ineffective, then brain stimulation therapies such as ECT is used, according to Dr. Marchionni[4]. Recently, refinement in ECT has been made in this area to enable this procedure to be more commonly performed as an outpatient procedure[5]. What is ECT and how does it work? ECT deliver as series of high frequency electrical pulses to to the non-dominant right or left hemisphere. Thus, repetitive electrical stimulation over the cortex results in an entrainment of pyramidal cell firing with subsequent generalisation of cortical activity and production of a generalised tonic-clonic seizure, which is usually self-limiting within 30-60 seconds[4]. However, he argued that ECT remains underutilised due to its limited availability, social stigma, and concerns regarding the adverse effect on the cognitive function[5]. Other upcoming treatment modalities for TRD includes the use of repetitive transcranial

magnetic stimulation (rTMS) which has shown to be effective in TRD patients since focused pulses of an electromagnetic coil are continuously discharged over the scalp to stimulate the cortical neurons and alter neural excitability without causing seizures[4,6]. Regarding the efficacy of rTMS in patients with TRD, Dr. Marchionni shared a study by Holtzheimer *et al*., (2010) that evaluated the advantage of rTMS in TRD patients. 14 TRD patients with a median age of 51 years were included in the study. Among these, 1 was diagnosed with bipolar 2 disorder. The results highlighted the effectiveness of TMS since it significantly reduced the symptoms of deperssion and anxiety. More importantly, the improvement persisted for 3-6 weeks post-treatment; however, 1 patient experienced serious adverse event (increased suicidal ideation), and 2 patients failed to complete the full course of treatment[7]. Despite the positive findings reported by this study, a more recent meta-analysis by Yu *et al*., (2024) concluded that a higher doses of rTMS is not necessarily better in treating patients with TRD, compared to an intermediate or lower dose of rTMS. Here, Dr. Marchionni suggested that a precise dose-response relationship requires further evaluation to determine the effective dose of rTMS in patients with TRD.[8]

Ketamine Saves the Day!

Over the last two decades, ketamine has emerged as a promising treatment for TRD[9] since ketamine affects multiple neurotransmitters and their receptors, particularly the N-methyl-D-aspartate (NMDA) receptors. Nonetheless, the precise mechanism of ketamine's antidepressant activity remains elusive[10], but the antidepressant activity of ketamine may possibly be related to several of its metabolites (norketamine and hydronorketamines)[11]. So what does this means? Dr. Marchionni shared his view on this and explained that ketamine seems to be an attractive alternative for patients with depression because it is generally easier to administer compared to ECT and is not associated with significant retrograde amnesia. However, he reminded us that ketamine is a schedule III medication with a potential for abuse, this may limit its applicability in clinical practice[5]. But how effective is ketamine when compared to ECT for TRD? An open-label, randomised noninferiority trial by Anand *et al*., (2023) compared the effectiveness of the ketamine with that of ECT in patients with TRD.

365 patients were randomised to receive either ketamine (0.5 mg per kilogram of body weight over 40 minutes) twice per week (n=195) or ECT three times per week (n=170). The primary outcome was a response to treatment (decrease of ≥50% from baseline score on the 16-item Quick Inventory of Depressive Symptomatology-self-report). The secondary outcome included scores on memory test and patient-reported quality of life[5]. Remarkably, the results revealed a total of 55.4% of patients in the ketamine group and only 41.2% in the ECT group had a treatment response (difference of 14.2 percentage points; 95% confidence interval [CI], 3.0 to 24.2; p<0.001 for the noninferiority of ketamine to ECT)

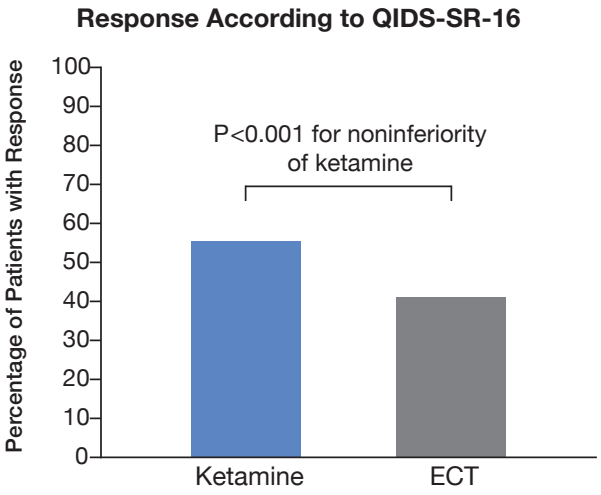


Figure 1. *Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) between ketamine and ECT groups*[5].

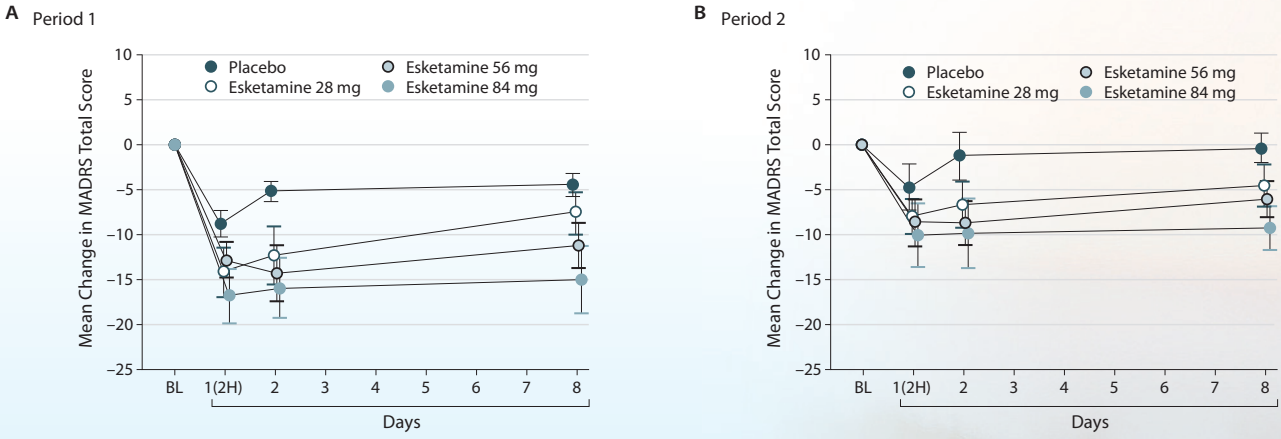
(**Figure 1**). Even more importantly, ECT was reported to be associated with a decrease in memory recall after 3 weeks of treatment with gradual recovery during follow-up. The study concluded that ketamine was noninferior to ECT as therapy for TRD without psychosis[5]. Dr. Marchionni reiterated that even though these findings are promising, questions still remains whether ketamine is effective in different population group (older adults vs adolescents), effective administration routes (intravenous vs tablet), and the precise dosage required (high vs low) for therapeutic effects.

From Chaos to Calm with Esketamine

TRD is a challenging since individuals with TRD often experience prolonged depressive episodes, which can lead to treatment discontinuation prior to reaching recovery, according to Dr. Marchionni. As a result, they may find it difficult to socialise and seek employment[12]; therefore, effective and specific treatments for TRD is urgently required. Esketamine (ESK), which is a non-competitive NMDA receptor antagonist may help fulfil the unmet treatment needs in TRD since several real-world studies have demonstrated the benefit of ESK treatment in adult patients with TRD[12]. Dr. Marchionni shared the findings from a phase 2, double-blind, doubly randomised, delayed-start, placebo-controlled study that evaluated the efficacy, safety, and dose-response of intranasal ESK in patients with TRD. Notably, the study consisted of 4 phases (screening, double-blind treatment [days 1-15], optional open-label treatment [days 15-74], and post-treatment follow-up [8 weeks]. Moreover, during period 1, participants were randomised (3:1:1:1) to placebo (n=33), ESK 28 mg (n=11), 56 mg (n=11), or 84 mg (n=12) twice weekly[13].

Subsequently in period 2, 28 placebo-treated participants with moderate-to-severe symptoms were re-randomised (1:1:1:1) to 1 of the 4 treatment arms and those with mild symptoms continued to receive placebo. Interestingly, all participants continued their antidepressant throughout the study period. The primary efficacy endpoint was the change from baseline to day 8 (each period) in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. Among 67 participants, the change in MARDS total score (both periods combined) in all 3 ESK groups was superior to placebo (p<0.001), with a significant ascending dose-response relationship (p<0.001) (**Figure 2**). The findings from this study suggests that intranasal ESK provides a rapid onset symptomatic relief, and the response persists for more than 2 months with a lower dosing frequency[13]. Similarly, findings from the phase 3, open-label study (SUSTAIN-2), demonstrated ESK nasal spray added to oral antidepressant therapy improved the depression in TRD patients[14]. Considering guideline-supported antipsychotic augmentation agents are often used in TRD patients, is ESK suitable for augmentation compared to these agents? An open-label, single-blinded, multicenter, phase 3b, randomised, active controlled trial evaluated the efficacy and safety of ESK nasal spray with extended-release quetiapine augmentation therapy, both in combination with ongoing treatment with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) in patients with TRD[15].

The primary endpoint was remission, defined as a score of 10 or less on the MADRS, at week 8 (scores ranging from 0-60, with higher scores indicative of more severe depression)[15]. The

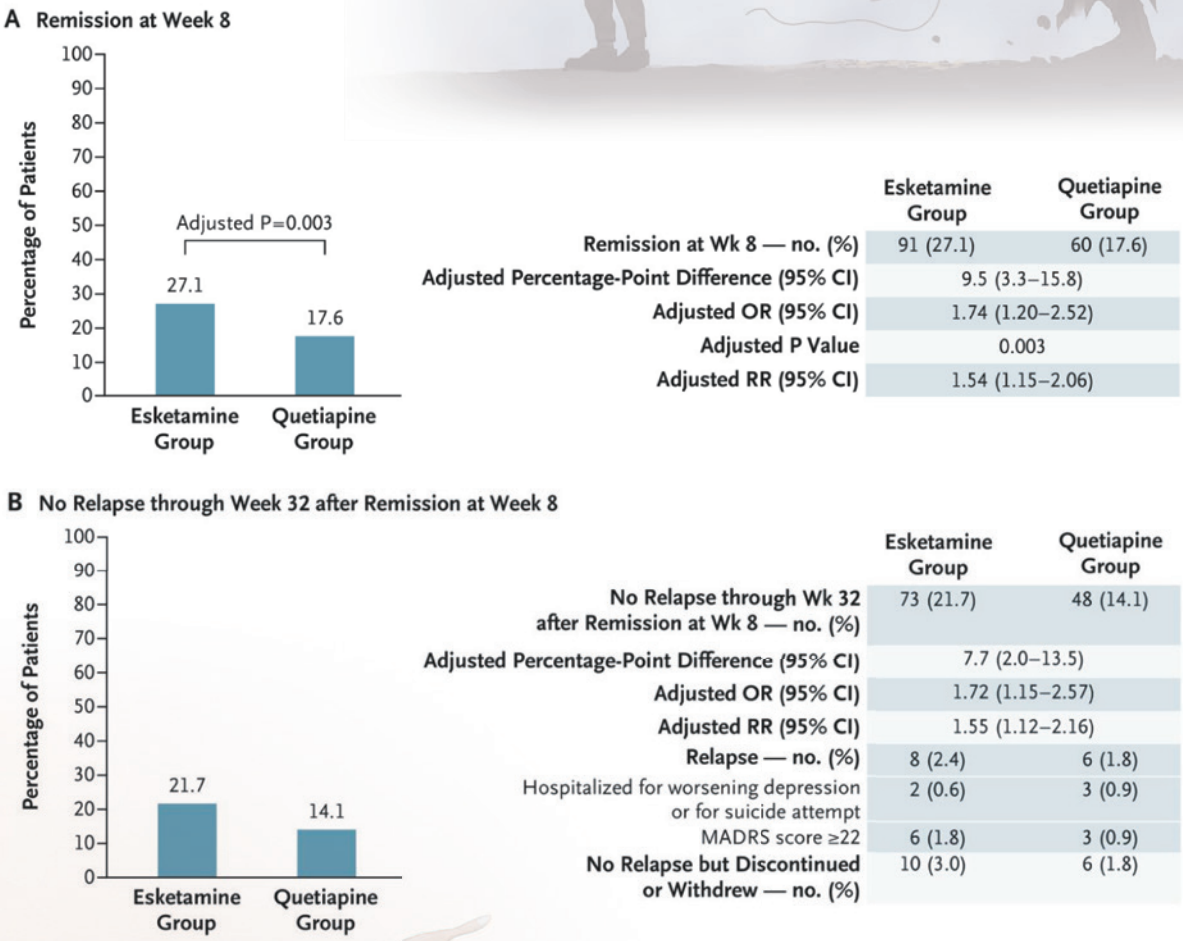


No. of participants				
Placebo	33	33		33
Esketamine 28 mg	11	11		11
Esketamine 56 mg	11	11		11
Esketamine 84 mg	12	12		12

No. of participants				
Placebo	6	6		6
Esketamine 28 mg	8	8		8
Esketamine 56 mg	9	9		9
Esketamine 84 mg	5	5		5

Figure 2. *Mean Change in Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score Over Time in Double-Blind Phase. Changes shown in periods 1 (A) and 2 (B). Period 2 consisted only of participants who had received placebo in period 1 and had moderate to severe symptoms (n = 28). Period 1 (days 1-8) and period 2 (days 8-15) are discussed in the Design section of the Methods and shown in the vertical axis of Figure 1. BL indicates baseline; 2H, 2 hours post dose. Error bars indicate standard error (SE)*[13].

key secondary endpoint was no relapse through week 32 after remission at week 8. Analysis of the primary and secondary endpoints were adjusted for age and number of treatment failure. 336 patients were randomised to ESK and 340 to quetiapine. Astonishingly, more patients on ESK had remission as early as week 8 (27.1%) compared to those on quetiapine (17.6%), (p=0.003) (**Figure 3**). More importantly, these patients had no relapse through week 32 after remission at week 8 (21.7% ESK group vs 14.1% quetiapine group). These findings suggest that patients with TRD treated with ESK intranasal spray plus an SSRI or SNRI have better remission rate (as early as 8 weeks) compared to extended-release quetiapine plus an SSRI or SNRI[15]. In conclusion, Dr. Marchionni suggested that ESK is a stepping stone toward controlling symptoms of TRD, however, clinicians are strongly encouraged to identify MDD patients at risk of developing TRD early so they can be referred to specialist for further evaluation.



	Esketamine Group	Quetiapine Group
Remission at Wk 8 — no. (%)	91 (27.1)	60 (17.6)
Adjusted Percentage-Point Difference (95% CI)	9.5 (3.3–15.8)	
Adjusted OR (95% CI)	1.74 (1.20–2.52)	
Adjusted P Value	0.003	
Adjusted RR (95% CI)	1.54 (1.15–2.06)	

	Esketamine Group	Quetiapine Group
No Relapse through Wk 32 after Remission at Wk 8 — no. (%)	73 (21.7)	48 (14.1)
Adjusted Percentage-Point Difference (95% CI)	7.7 (2.0–13.5)	
Adjusted OR (95% CI)	1.72 (1.15–2.57)	
Adjusted RR (95% CI)	1.55 (1.12–2.16)	
Relapse — no. (%)	8 (2.4)	6 (1.8)
Hospitalized for worsening depression or for suicide attempt	2 (0.6)	3 (0.9)
MADRS score ≥22	6 (1.8)	3 (0.9)
No Relapse but Discontinued or Withdrew — no. (%)	10 (3.0)	6 (1.8)

Figure 3. *Primary and Key Secondary End Points. Panel A shows the percentage of patients with remission (primary endpoint) in the two trial groups; the esketamine group and the quetiapine group. Remission was defined as a score of 10 of less on the Montgomery–Åsberg Depression Rating Scale (MADRS; scores range from 0 to 60, with higher scores indicating more severe depression) and no treatment or study discontinuation before week 8. Panel B shows the comparison of the two trial groups with respect to freedom from relapse through week 32 after having remission at week 8, without treatment or study discontinuation (key secondary endpoint),, as well as the number of patients who had a relapse and the number of patients who remained free from relapse through week 32 after having remission at week 8 but who discontinued treatment. CI = confidence interval*[15].

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by Eura So

Therapeutic Treatments to Cope with a Love Breakup

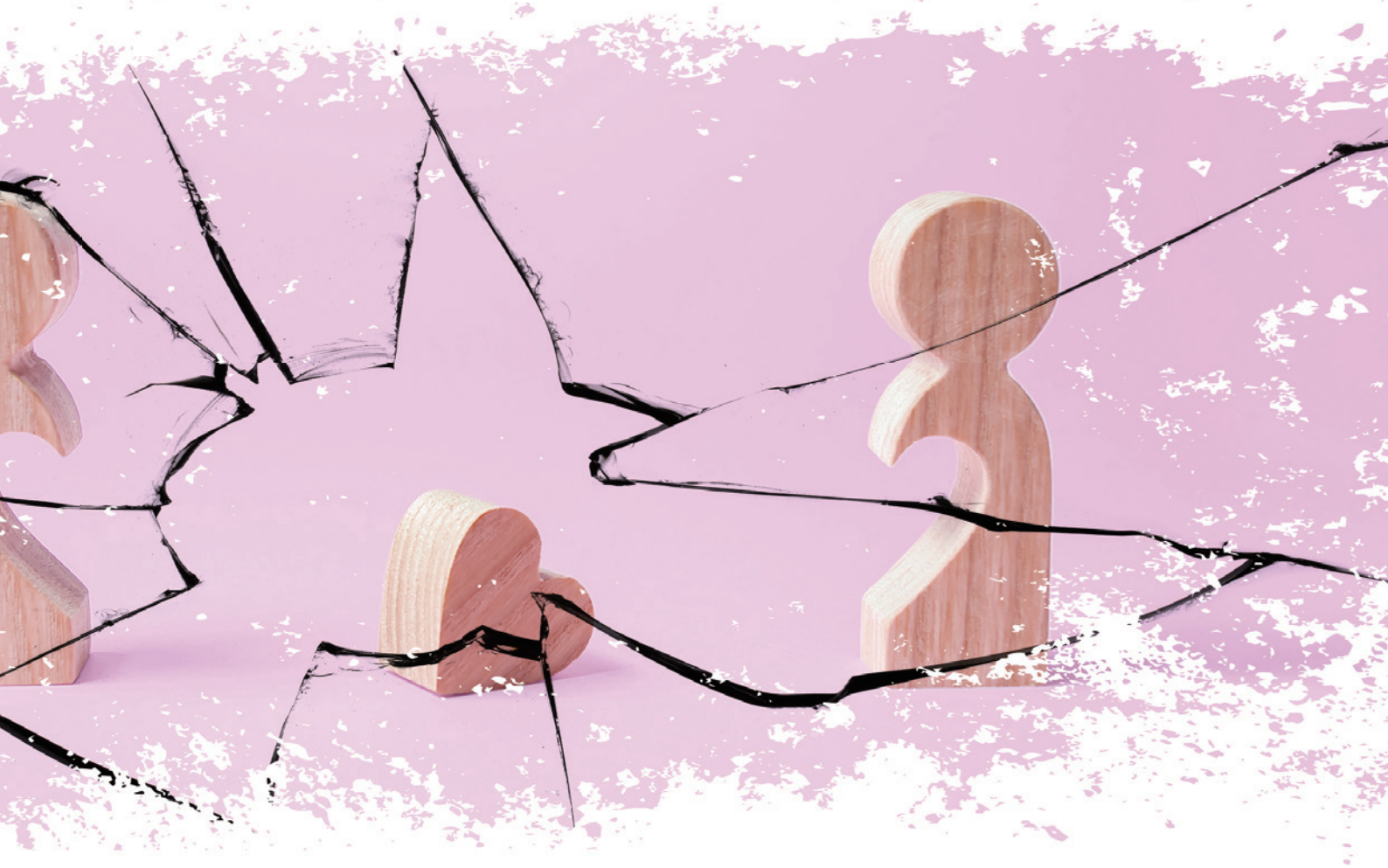
"The hottest love has the coldest end." Facing a romantic relationship breakup can be devastating, overwhelming and heart-wrenching. There has been an increasing trend of divorce over the last 3 decades in Hong Kong, with the crude divorce rate (per 1,000 population) surging staggeringly from 1.11 in 1991 to 2.14 in 2020, as documented by the Census and Statistic Department[1]. It appears that getting a divorce has become a checklist item that people follow from cradle to grave. A romantic breakup can result in breakup distress, betrayal and heartbreak[2]. The emotional agony of a broken heart can manifest as the love trauma syndrome, affecting individuals' functionality and may trigger feelings of depression, rumination, anxiety and love grief[3].More importantly, it was reported that a significant association was found between commitment to a romantic relationship and suicidal risk among individuals who had experienced a break-up within the last 3 months, especially when affected by depression[4]. The statistics indicate that the love distress affects a broad population group, leading to the consideration of this situation as a public health issue[3]. When the once-celebrated lifelong commitment leaves only love trauma, here are some science-proven therapeutic approaches that may help.

Physiological Changes in Response to a Romantic Relationship Breakup

The physiological changes related to a romantic relationship breakup are not merely confined to the heart, instead, it may include a cascade of changes that are both psychological and physical. Generally, breakup distress may lead to physical problems such as broken heart syndrome[2]. This acute pain, also known as stress cardiomyopathy or "takotsubo cardiomyopathy", may mimic symptoms of a myocardial infarction[5]. However, unlike actual myocardial infarction, those with broken heart syndrome typically recover faster and tests often reveal patient having normal coronary arteries, although some investigators have recorded cardiac contractile abnormalities and heart failure following acute emotional stress for a few weeks[2,6]. The transient stunning of the heart may also be caused by the spasm-related reduced perfusion secondary to increased catecholamines release from the blood circulation[7]. Moreover, some studies have suggested that both social and physical pain activate the same region of brain cortex[8]. For instance, a neuroimaging study found that the right ventral prefrontal cortex (RVPFC) is activated during painful stimulation of both physical and social pain, with greater RVPFC activation being associated with less pain[9]. Additionally, another study on recent unwanted break-ups using functional Magnetic Resonance Imaging (MRI) revealed that the sensory areas for physical pain were activated when the participants viewed a photograph of their ex-partner[10]. The authors then compared their data with over 500 published studies and concluded that both social and physical pain activated the somatosensory cortex and the dorsal posterior insula, further supporting that social rejection and physical pain share similar distressing activated pathways[10].

Acetaminophen – Does that Work for Social Pain?

Given that both social and physical pain share overlapping physiological and neural mechanisms, it undoubtedly raises the question of whether physical painkillers can work effectively on alleviating social pain as well. Acetaminophen, one of the most commonly prescribed physical pain suppressants that acts through central neural mechanisms, has been used by Dewall *et al*. to study its effects on reducing behavioural and neural responses associated with the pain of social rejection[11]. A total of 30 participants were instructed to take one 500 mg acetaminophen pill after waking up and before bed each day while 32 participants took the same dose of a placebo for a period of 21 days. All participants were required to fill in the Hurt Feeling Scale each evening to report how much social pain they had encountered that day in terms of the experience of social exclusion, as well as to provide a daily measure of general positive emotion they had experienced during the same day[11]. Remarkably, it was found that participants who took daily acetaminophen showed a significantly reduction in hurt feelings over time while those who took the placebo showed no change over time in their daily hurt feelings[11]. More specifically, from Day 9 to Day 21, participants in the acetaminophen group reported significantly lower daily hurt feelings on average than those in the placebo group while both groups demonstrated no effect on daily positive emotions[11]. Additionally, Dewall *et al*. have also examined



the neural mechanisms by which acetaminophen reduces hurt feelings through conducting a neuroimaging study. A total of 25 participants completed the social exclusion task while undergoing an fMRI scan, with 10 participants taking 2000 mg acetaminophen daily and 15 taking placebo. In the social exclusion task, participants believed that they would participate in a virtual ball-tossing game with two other same-sex participants, which was, in fact, a preset computer program that included them in the first round and then excluded them in second round after receiving the ball three times. After that, participants were required to complete a measure of self-reported social distress for assessing their feelings in response to the exclusion episode. The region-of-interest (ROI) analyses and the whole-brain analyses revealed that participants who took acetaminophen showed significantly lower activity in the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula – regions previously shown to respond to social pain – in response to social exclusion versus inclusion (**Figure 1**)[11]. This

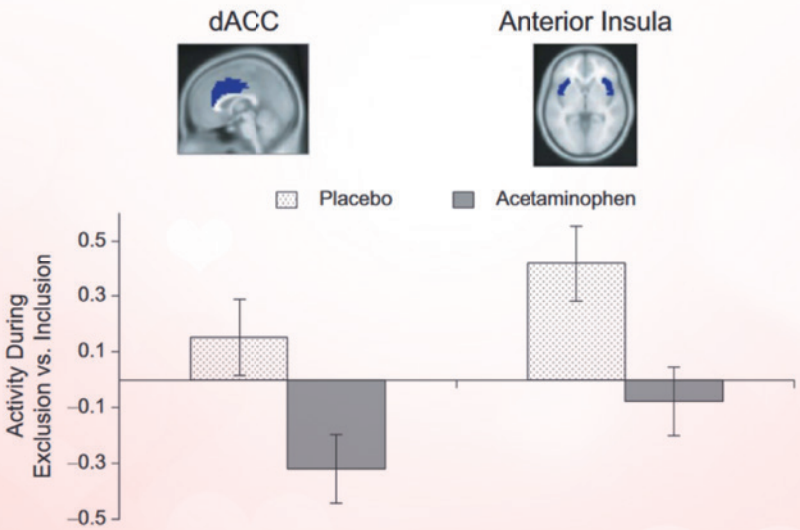


Figure 1. Change in neural activity during social exclusion vs. social inclusion in the dorsal anterior cingulate cortex (dACC; left) and bilateral anterior insula (right) in participants who took acetaminophen and those who took placebo, error bars represent standard error[11].

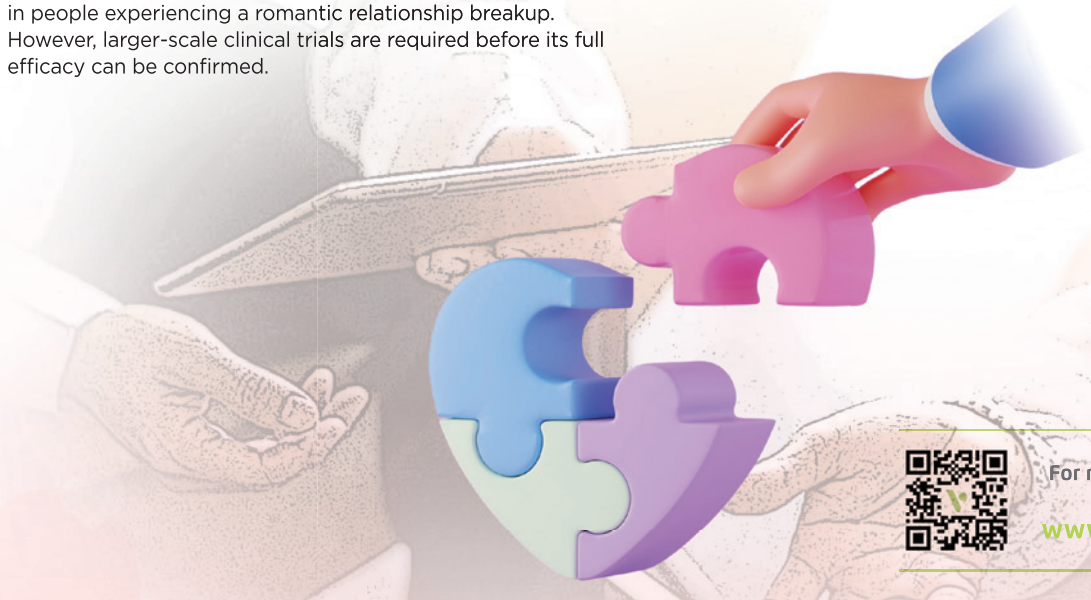
study suggested that this over-the-counter painkiller can at least temporarily mitigate social-pain-related distress, however, further research with a larger population size is warranted to verify the potential benefits of acetaminophen in reducing emotional responses to social rejection.

A Promising Breakthrough in Managing the Love Trauma Syndrome

It may not seem feasible to take daily acetaminophen for treating your social pain especially when acetaminophen is only effective from day 9 onwards[11]. Recently, a group of researchers from Iran had come up with a new idea: treating the love trauma syndrome with intensified electrical stimulation[12]. Alizadehgoradel *et al*. conducted a randomised, sham-controlled, single-blind parallel trial involving 36 participants with love trauma syndrome to receive transcranial Direct Current Stimulation (tDCS) on the left dorsolateral prefrontal cortex (DLPFC), the right ventrolateral prefrontal cortex (VLPFC) or sham stimulation in a 1:1:1 ratio (20 mins, twice-daily sessions with 20 mins intervals for 5 consecutive days)[12]. The primary outcome focused on the effects of the intervention on love trauma syndrome and neuropsychological performance, as measured by the Love Trauma Inventory (LTI) questionnaire, the positive and negative affect schedule (PANAS) and the Emotion Regulation Scale (DERS) etc. Post hoc comparisons revealed that both two tDCS montages, targeting either the left DLPFC or right VLPFC, significantly reduced love trauma syndrome symptoms immediately after and at 1-month follow-up after intervention[12]. Notably, the reduction was significantly greater in the DLPFC group compared to the VLPFC group[12]. Furthermore, there was significant improvement in anxiety, depressive state, and emotional regulation in participants after receiving tDCS in both active stimulation conditions compared to the sham group[12]. This study demonstrated a promising therapeutic intervention with potential clinical implications for improving emotional regulation and symptoms of love trauma syndrome in people experiencing a romantic relationship breakup. However, larger-scale clinical trials are required before its full efficacy can be confirmed.

What Else Works for Dealing with a Love Breakup

Given the availability of equipment and operators, it may not be realistic to receive intensified electrical stimulation for curing heartbreak at this time. Fortunately, there are other accessible therapeutic interventions that are effective as well. Peñuñuri *et al*. has conducted a systematic review on the therapeutic treatments being examined to cope with a love breakup from 1992 to 2023 in Spanish, English and Protuguese[3]. Out of 156 records from the internet, 13 articles were selected to address the effectiveness of the studied intervention, excluding those that were theoretical or not intervention studies. In general, the objectives of these intervention studies were to deal with a series of severe symptoms affecting people's functionality and maladaptive responses generated after suffering a love break up, such as anguish, depression symptoms, anxiety, rumination, love grief and love trauma syndrome[3]. It was reported that cognitive behavioural therapy (CBT), which involves elements of psychoeducation, empathy, stress management, identifying personal needs, restructuring on dysfunctional attribution of loss, strengthening self-love and managing cognitive distortion etc., was exclusively used and can significantly reduce mental health problems, including depression and anxiety. One study also showed that 6 sessions of Hatha yoga and mindfulness meditation can statistically reduce rumination associated with love breakups in the experimental group compared to the control group[13]. Interventions on emotional symptomatology and aspects such as self-esteem also showed favourable effect as a psychological treatment for love grief[3]. In conclusion, a love breakup may be unavoidable, but love trauma syndrome is curable. Time heals, as well as acetaminophen, intensified electrical stimulation on DLPFC and VLPFC, and cognitive-behavioral therapy. Above all, there are always more solutions than problems, thus, never give up on having a happy life.



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‡ vs placebo on top of maximally tolerated statins.[7]

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LDL-C: low-density lipoprotein cholesterol.

Abbreviated Prescribing Information
Nilemdo (bempedoic acid) tablets 180 mg. **Indications:** Nilemdo is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. **Dosage and Administration:** Administer 180 mg orally once daily with or without food. **Contraindications:** None. **Warnings and Precautions:** *Hyperuricemia:* May increase blood uric acid levels. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. *Tendon Rupture*: Nilemdo is associated with an increased risk of tendon rupture or injury. Discontinue Nilemdo at the first sign of tendon rupture. Avoid Nilemdo in patients who have a history of tendon disorders or tendon rupture. Pregnancy and lactation. **Adverse Reactions:** *Most common:* upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Others include tendon rupture, gout, benign prostatic hyperplasia, atrial fibrillation. **Drug Interactions:** *Simvastatin:* Avoid concomitant use of Nilemdo with simvastatin greater than 20 mg. *Pravastatin:* Avoid concomitant use of Nilemdo with pravastatin greater than 40 mg. Version: Mar 2023.

Nustendi (bempedoic acid and ezetimibe) tablets 180 mg bempedoic acid/10 mg ezetimibe. **Indications:** Nustendi is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. **Dosage and Administration:** Administer one tablet (180 mg bempedoic acid and 10 mg ezetimibe) orally once daily with or without food. Swallow the tablet whole. Coadministration with Bile Acid Sequestrants: Administer at least 2 hours before or at least 4 hours after bile acid sequestrants. **Contraindications:** Known hypersensitivity to ezetimibe tablets. **Warnings and Precautions:** *Hyperuricemia:* May increase blood uric acid levels. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate. *Tendon Rupture:* Increased risk of tendon rupture or injury. Discontinue Nustendi at the first sign of tendon rupture. Avoid Nustendi in patients who have a history of tendon disorders or tendon rupture. Pregnancy and lactation. **Adverse Reactions:** *Most common:* upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, and influenza. Others include tendon rupture, gout, benign prostatic hyperplasia, atrial fibrillation. **Drug Interactions:** *Simvastatin:* Avoid concomitant use of Nustendi with simvastatin greater than 20 mg. *Pravastatin:* Avoid concomitant use of Nustendi with pravastatin greater than 40 mg. *Cyclosporine:* Monitor cyclosporine concentrations. *Fibrates:* If cholelithiasis is suspected in a patient receiving Nustendi and fenofibrate, consider alternative lipid-lowering therapy. *Cholestyramine:* Administer Nustendi either at least 2 hours before or at least 4 hours after bile acid sequestrants. Version: Mar 2023.

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HK-DAI-NN-2307005
Date of Approval: Jul 2023

by Jasmine Lai

Clinical Strategies on Prescribing Long-acting Injectable Antipsychotics in Managing Schizophrenia

Schizophrenia is a psychiatric syndrome of delusions, disorganised speech, hallucinations, and impaired executive functioning[1]. Despite affecting approximately 1% of the global population, poor treatment adherence remains as an unmet need associated with worse clinical outcomes[1,2]. In the scientific symposium organised by Janssen Pharmaceuticals on the 12th of March 2024, two renowned experts in Psychiatry shared their clinical strategies for long-acting injectable (LAI) utilisation in managing schizophrenia patients.

Dr. Rebecca Roma

Medical Director,
REACH, Living Learning Communities Adjunctive (LLC) Faculty,
University of Pittsburgh,
School of Medicine Pittsburgh,
Pennsylvania

Dr. Chang Wing Chung

Clinical Associate Professor,
Department of Psychiatry,
School of Clinical Medicine,
University of Hong Kong

Relapse Worsens Cognitive Functioning and Treatment Responses

First-episode psychosis (FEP) in schizophrenia is characterised by a high antipsychotic therapy response rate, followed by frequent antipsychotic discontinuation and elevated relapse rates soon after maintenance treatment begins[3]. Dr. Roma explained that the serious neurobiological adverse effects of psychotic relapse - including neuroinflammation and oxidative stress - may explain the atrophic changes observed during early FEP (**Figure 1**)[3]. In fact, in an observational study, Cahn *et al.* (2002) reported a progressive loss of global grey matter in schizophrenic patients after the first episode that was related not only to the disease process, but also to antipsychotic treatment use[4].

Dr. Roma explained that there is a strong correlation between further relapses and increased treatment resistance[5]. The study by Takeuchi *et al.* (2019) further highlighted a significant decline in treatment response at the second episode of schizophrenia compared with the first episode (50% response rate episode 1 vs. episode 2: 10.4% vs 48.7% [week 7]; 27.8% vs 88.2 [week 27], respectively, **Figure 2**)[5], suggesting the importance of utilising effective treatment as early as possible in patients with schizophrenia.

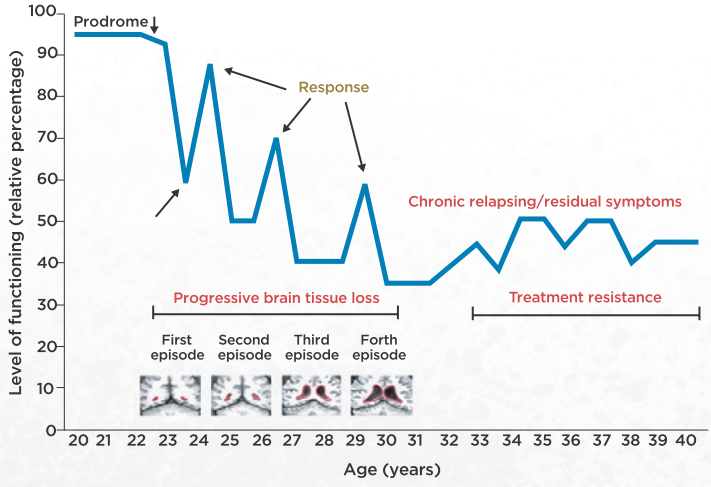

Figure 1. Schizophrenia disease progression[3].

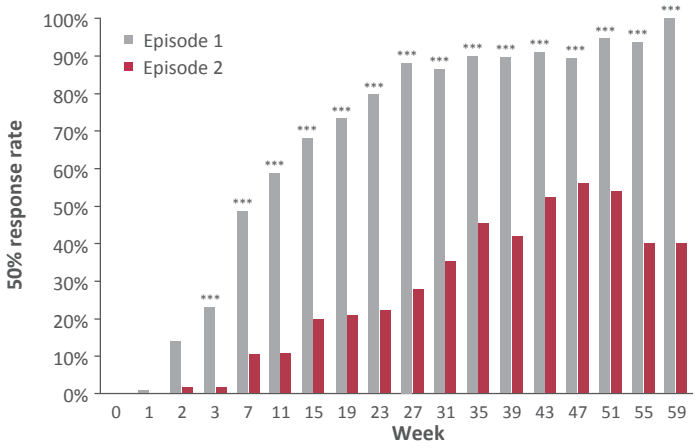

Figure 2. *Changes in 50% response rates over time in first vs second episodes[5], ***p<0.001, **p<0.01.*

The Primal Factors Hindering Optimal Outcomes

However, the challenge in managing schizophrenia is not solely dependent on treatment effectiveness. Dr. Roma shared the data from a meta-analysis of 29 studies by Alvarez-Jimenez *et al*. (2012), where medication nonadherence attributed to a four-fold increased risk for relapse in patients with FEP, followed by persistent substance use disorders (3-fold), caregivers' excessive criticism (2.3-fold) and poorer premorbid adjustment (2.2-fold) (**Figure 3**)[6].

In practice, Dr. Roma highlighted that both patients and healthcare professionals may experience reluctance towards LAIs. In the cross-sectional study by Cahling *et al*. (2017), although patients were concerned that they were obliged to show up at clinics regularly and would experience reduced treatment autonomy, mental healthcare professionals may also overestimate patients' fears of LAIs, and the expressed fears exceeded the actual experiences of patients already on LAIs[7].

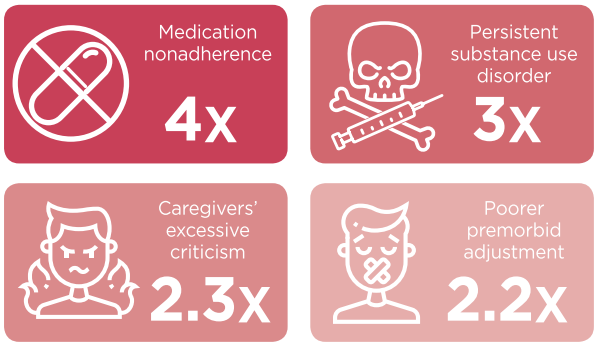

Figure 3. *Risk factors for relapse following treatment for first episode psychosis[6]. Adapted from Alvarez-Jimenez et al. 2012.*

Paliperidone Palmitate – An Effective LAI Improving Medication Adherence and Clinical Outcomes

Dr. Roma outlined that LAIs overcome certain challenges faced by patients taking oral antipsychotics. She highlighted the findings of an analysis of United States (US) medical claims data by Pilon *et al*. (2017), where patients initiated on second-generation (SG) LAIs, particularly paliperidone palmitate, were more likely to be adherent to their medication than those on oral atypical antipsychotics (OAAs) as reflected by a higher odds of proportion of days covered (PDC) ≥80% (odds ratio [OR]: 1.28, $p<0.001$, **Figure 4**)[8].

Apart from improved adherence, a meta-analysis by Lin *et al*. (2021) demonstrated that LAIs were also associated with reduced hospitalisations (OR: 0.62) and emergency room admissions (incidence rate ratio [IRR]: 0.86) compared to oral antipsychotics. The higher pharmacy costs were offset by these lower medical costs, resulting in a non-significant difference in total healthcare costs[9]. Notably, Pilon *et al*. (2017) also found that paliperidone palmitate was the only LAI with statistically significant medical cost savings (mean monthly cost difference: -$225 USD, $p<0.001$)[8].

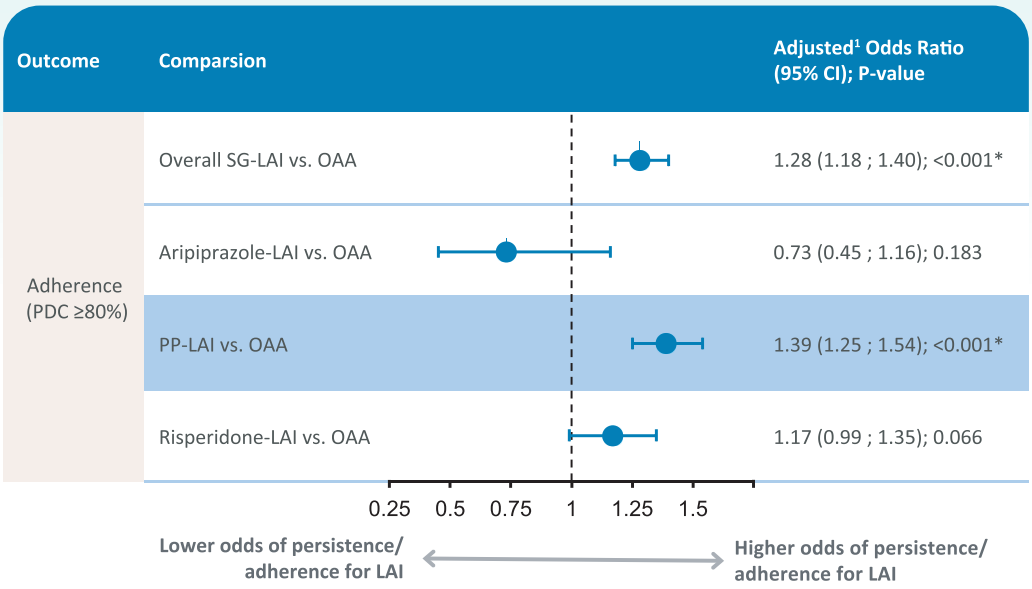

*Figure 4. Adjusted comparison of adherence in Medicaid beneficiaries between LAIs and OAAs[8], CI: confidence interval, LAI: long-acting injectable, OAA: oral atypical antipsychotic, PDC: proportion of days covered, PP: paliperidone palmitate, SG: second generation, *p<0.001.*

The Exceptional Performance of Twice-Yearly Paliperidone Palmitate

Three dosing regimens of paliperidone palmitate are available, namely once-monthly (PP1M), once-quarterly (PP3M), and twice-yearly (PP6M), with extended- dosing formulas retaining high efficacy and safety[10]. A randomised controlled trial (RCT) involving 702 patients with schizophrenia by Najarian *et al*. (2022) demonstrated that 92.5% of patients receiving PP6M remained relapse-free at 1 year, which was non-inferior to PP3M (95.1%, **Figure 5**). Furthermore, the incidences of treatment-emergent adverse events were similar between PP6M (62.1%) and PP3M (58.5%) with no new safety concerns[10]. Dr. Roma concluded that the clinical data supported the sustained efficacy of PP6M in controlling relapse in schizophrenia, with the potential to further enhance patients' medication adherence.

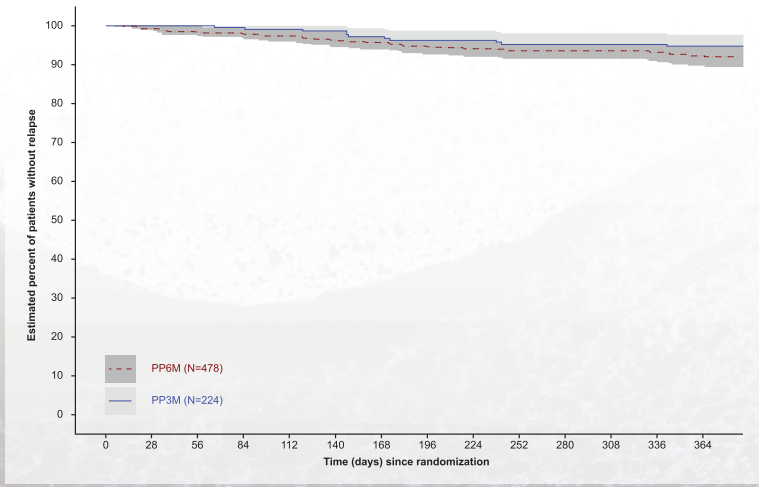

Figure 5. Percentage of patients without relapse[10].

Managing Schizophrenia with Paliperidone Palmitate in Practice

To understand the practical benefits of paliperidone palmitate and switching to extended-dosing regimens, Dr. Roma shared a case of a 26-year-old male with schizophrenia that she had previously treated.

Case presentation:

- A 26-year-old male pharmacist was diagnosed with schizophrenia in his early 20s. He was initially prescribed oral risperidone 4 mg by a different provider but reported to have missed doses several times per week. Moreover, the patient resigned from his job and began to experience an increased paranoia. In addition, he also started to smoke cigarettes and was reported to have become more poorly kempt as he often rummaged through trash containers.

Treatment and outcomes:

- PP1M 100 mg was initiated with the encouragement of his family and the patient showed good stability. 8 months later, he then switched to PP3M 350 mg and took up a career as a pharmacy technician. Since the patient remained clinically stable with no reported adverse events, he was eventually switched.

Addressing Questions about Longer Dose LAIs- Dr. Roma's Experience

Dr. Roma summarised the utilisation of LAIs by detailing the possible concerns and her strategies for managing such treatment.

Will patient follow-up be less frequent than every 6 months?

- In the non-inferiority RCT, 87% of patients with schizophrenia completed the study[10], showing that these patients maintain a high frequency of follow-up. Providers must also continue monitoring relapse or breakthrough symptoms and the other medications schizophrenia patients receive over the 6 months.

What happens when patients are hospitalised and receive additional paliperidone palmitate injections?

- There is no increased risk for patients with schizophrenia as paliperidone palmitate's insoluble, slow-dissolving formula allows stable blood concentrations without incurring additional side effects[11].

How are breakthrough symptoms managed?

- Breakthrough symptoms are often traced back to inappropriate injection administration. Moreover, flexibility with early/late dosing, gluteal injection options for longer half-lives, and oral medication supplemented as needed may enhance the efficacy of PP-LAIs if necessary.

Which patients are ideal for extended-dosing formulas?

- The ideal patient for PP6M is young, high functioning, with good insight and with good family support.

How can healthcare providers empower their patients in accepting treatment?

- Communicate the value of treatment early in the course of their disease. Providers can show patients brain scan images and explain the potential dose reductions after starting PP1M instead of emphasising the injection procedure. Weiden *et al*. (2015) reported that the proportion of patients willing to try LAIs increased from 48% to 96% after psychiatrists explained the values of LAIs[12].

Local Experience and Salient Points in Managing Schizophrenia with LAIs

Dr. Chang illustrated the local scenario in managing schizophrenia and shared his advice on using LAIs in practice. Like Dr. Roma, he noted that LAIs may address treatment nonadherence: "patients initiated on PP6M should demonstrate good clinical responses, tolerability and stability on PP1M or even PP3M," he remarked. Furthermore, PP6M may be suitable for patients with a good functional status (i.e. with a full-time job) or have good insight into their illness.

However, Dr. Chang emphasised that an extended dosing interval may not completely solve the issues related to treatment adherence. Psychiatric follow-up with reasonable intervals for monitoring remains paramount for identifying breakthrough symptoms and finetuning, especially during the initial phase of the treatment. "More frequent follow-up for clinical monitoring during the initial stage of switching to PP6M is required to ensure that tolerability and sustained treatment response is maintained," Dr. Chang accentuated.

For more information, please visit
www.vpulsehk.com

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CP-464359 Jul 2024

by Dr. Mohsin Roshan

A New Chapter of Giant Cell Arteritis Treatment with Upadacitinib

Giant cell arteritis (GCA), also known as temporal arteritis is a chronic inflammatory vasculitis that predominately affects large- and medium-sized arteries in individuals above the age of 50. More notably, GCA affects the cranial branches of the carotid arteries and the granulomatous nature of GCA contributes to the formation of vessel aneurysms[1]. In addition, untreated GCA may also lead to blindness, aortitis and stroke[2]. Not surprisingly, the highest incidence of GCA is reported in the Northern Europe and the lowest in Asia-Pacific[2]. Traditionally, patients with GCA are treated with a high dose of corticosteroids, but since corticosteroids are associated with significant side effects[3], the treatment unmet needs persist in patients with GCA until recently.

Giant Cell Arteritis: A Silent Predator

GCA is a medium and large-vessel vasculitis, which is an important cause of secondary headache in older adults ≥ the age of 50. While GCA has a classic presentation, atypical presentation such as fever of unknown origin, cough, low or normal erythrocyte sedimentation rate [ESR]) may lead to a delay in diagnosis[4]. Interestingly, the primary vascular targets of GCA are extracranial branches of the external and internal carotid arteries which results in headaches, scalp tenderness and jaw claudication. If left untreated, it may potentially lead to blinding ischaemic injury to the optic nerve or retina[5]. In fact, at least 9% of patients experience severe, irreversible vision loss from the disease, a complication that is more likely if high dose corticosteroid are not started early[5]. To assist the diagnosis of GCA, the 2022 American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) provided a classification criterion for GCA with an 87% sensitivity and 94.8% specificity (**Figure 1**)[6].

2022 AMERICAN COLLEGE OF RHEUMATOLOGY / EULAR

CLASSIFICATION CRITERIA FOR **GIANT CELL ARTERITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

ABSOLUTE REQUIREMENT	
Age ≥ 50 years at time of diagnosis	
ADDITIONAL CLINICAL CRITERIA	
Morning stiffness in shoulders/neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery[1]	+2
LABORATORY, IMAGING, AND BIOPSY CRITERIA	
Maximum ESR ≥ 50 mm/hour or maximum CRP ≥ 10 mg/liter[2]	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound[3]	+5
Bilateral axillary involvement[4]	+2
FDG-PET activity throughout aorta[5]	+2

Sum the scores for 10 items, if present. A score of ≥ 6 points is needed for the classification of GIANT CELL ARTERITIS.

Figure 1. The final 2022 American College of Rheumatology/EULAR classification criteria for GCA[6]. EULAR= European Alliance of Associations for Rheumatology, GCA= giant cell arteritis. ESR= erythrocyte sedimentation rate; FDG-PET= fluorodeoxyglucose-18-positron emission tomography.

However, temporal artery biopsy (TAB) remains the gold standard for the diagnosis of GCA and should be performed within 2 weeks of initiation of corticosteroids. What is the optimum time for obtaining a TAB in a patient suspected of GCA and is it necessary?

A study by Papadakos *et al*., (2023) analysed data from 109 patients with a median age of 76 years and a median time from glucocorticoid treatment to TAB of 4 days. Interestingly, 60% of biopsies were positive and the study suggested that steroid treatment for more than 7 days was independently linked with lower rates of positive TAB (adjusted odds ratio, 0.33; 95% confidence interval [CI], 0.11-1.00). What does this mean? This study demonstrated that glucocorticoid (GC) treatment may affect the results of TAB, especially if the biopsy is taken after 7 days[7]. But should patients suspected of GCA be treated with high or low dose of corticosteroids? The answer to this is often complicated since corticosteroids are often used as a mainstay treatment, however the type, dose, route and duration of corticosteroid still remains controversial. A study by Kanakamedala *et al*., (2021) surveyed neuro-ophthalmologists to determine the commonly prescribed dosage of corticosteroids for the treatment of GCA with or without visual loss. Remarkably, the study supported for conventional recommendations for high dose intravenous corticosteroid for GCA with visual loss and lower dose of oral regimens for GCA without visual loss (**Figure 2**)[8].

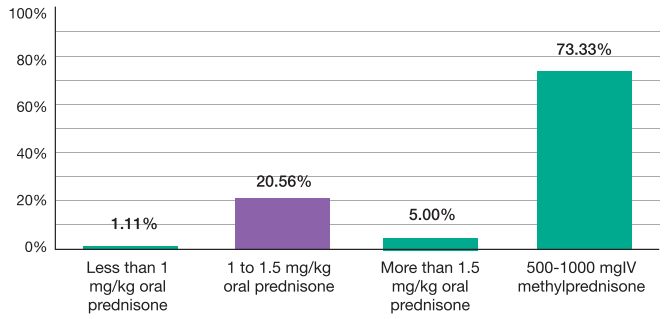

Figure 2. *Survey questions on dosage of corticosteroid used in patient with giant cell arteritis with acute visual loss[8]. IV= intravenous; kg= kilograms; mg= milligrams.*

A Breath of Fresh Air with Janus Kinase (JAK) inhibitors

Treatment for GCA has been limited and in the past since corticosteroids were the main treatment option. Nevertheless, recent studies have supported the use of JAK inhibitors (JAKi) since inflammatory markers such as interleukin-6 (IL-6) and interferon gamma (IFN-γ) have strongly been implicated in the pathogenesis of GCA[9]. One of the upcoming potential agents is the upadacitinib (UPA), an oral and selective JAKi

with multiple clinical indications and a strong inhibitory effects on IL-6 and IFN-γ. A double-blind, randomised placebo-controlled phase 3 trial conducted in 24 countries, consisting of two 52 weeks period evaluated the efficacy and safety of UPA with placebo in combination with GCs taper regimen in patients with GCA. The study included 428 patients randomised to receive either UPA 7.5 mg (UPA7.5 [n=107]) or UPA 15 mg (UPA15 [n=209]) or placebo (PBO [n=112]). The primary endpoint was sustained remission, defined as the absence of signs or symptoms of GCA from week 12 through week 52 and adherence to the protocol-defined GC taper regimen. Secondary endpoint included sustained complete remission (defined as achievement of sustained remission with normalised ESR and c-reactive protein [CRP]), disease flare-related endpoints and several patient-reported outcomes including the functional assessment of chronic illness therapy (FACIT)-Fatigue (a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function), and cumulative GC exposure[9].

Remarkably, the primary endpoint of sustained remission at week 52 was achieved in UPA15 group compared PBO group (46% vs 29%, p=0.0019). In addition, the study met 9 out of 11 multiplicity-controlled secondary endpoints with UPA15 including achievement of sustained complete remission from week 12 throughout week 52 (37% vs 16%, p<0.0001)[9]. Furthermore, UPA15 also reduced the risk of flare ups of GCA throughout the 52 weeks compared to those receiving PBO (**Figure 3**), as well as significantly improved the FACIT-Fatigue scores from baseline to week 52 (p=0.0036). However, even though UPA7.5 showed numerically better efficacy compared to placebo, the results were not as promising as those seen with UPA15. A salient point to note was the safety outcome related to UPA groups which were relatively comparative to PBO group, however, there were a higher rate of serious infection and major adverse cardiovascular events (MACEs) observed in PBO group with no MACEs reported in UPA groups. Here, the study highlighted the superior efficacy of UPA 15 mg in GCA when combined with a 26-week of GC taper dose, in addition to reducing the GC reliance when compared to placebo without causing any new safety signal concerns[9]. In light of these findings, we may conclude that the UPA 15 mg represents a potential new oral targeted therapy for patients with GCA, however, UPA is currently not an approved treatment for GCA and is awaiting for food and drug administration (FDA) approval.

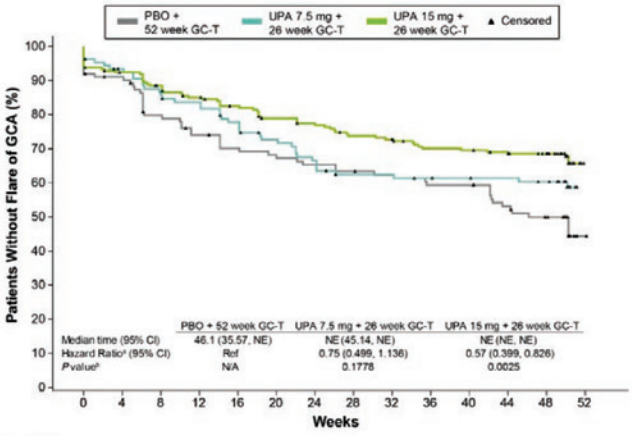

Figure 3. Kaplan-Meier Curves for Time to First Disease Flare Through Week 52. Patients who never met the "flare-free" criteria required prior to the assessment of disease flare were considered to have flare at baseline. Patients who met the "flare-free" criteria but did not have flares were censored at the last assessment prior to week 52[9]. GCA= giant cell arteritis, GC-T= glucocorticoid taper, NE= not estimable, PBO= placebo, UPA= upadacitinib

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Help patients with cGVHD

ROCK ON with REZUROCK®

(belumosudil) tablets

***First-in-class** ROCK2 inhibitor to treat **cGVHD**[1-3]*

featuring

RAP

Reduction of fibrosis[3]
Anti-inflammation[2,3]
Promising safety profile[1]

Meaningful Response

within a real-world demographic of cGVHD patients

ORR 75%[1,4,5,*]

Immunomodulator

to restore immune homeostasis with favorable safety[6]

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

NCCN Guidelines

Suggested Systemic Agent
for steroid-refractory cGVHD[7,†]

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)
† NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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
Presentation: REZUROCK (belumosudil) Tablets 200mg. **Indications:** For 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. **Dosage & Administration:** 200 mg given orally once daily until progression of chronic GVHD that requires new systemic therapy. Swallow REZUROCK tablets whole. Take REZUROCK with a meal at approximately the same time each day. If a dose of REZUROCK is missed, instruct patient to not take extra doses to make up the missed dose. Monitor total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) at least monthly. Modify REZUROCK dosage for adverse reactions including hepatotoxicity. Increase REZUROCK dosage to 200 mg twice daily when co-administered with strong CYP3A inducers or proton pump inhibitors. Avoid use in patients with moderate or severe hepatic impairment without liver GVHD. *For full dosage information, please refer to the full prescribing information*. **Contraindications:** None. **Precautions:** Based on findings in animals and its mechanism of action, REZUROCK can cause fetal harm when administered to pregnant woman. Advise pregnant women of the potential risk to fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during REZUROCK treatment and for one week after the last dose. **Drug Interactions:** Strong CYP3A Inducers and Proton Pump Inhibitors. **Pregnancy and lactation:** Advise pregnant women and females of reproductive potential of the potential risk to fetus. Because of the potential for serious adverse reactions from belumosudil in breastfed child, advise lactating women not to breastfeed during REZUROCK treatment and for one week after the last dose. Verify pregnancy status of females of reproductive potential prior to initiating REZUROCK treatment. **Undesirable effects:** Infections, asthenia, nausea, diarrhea, dyspnea, cough, edema, hemorrhage, abdominal pain, musculoskeletal pain, headache, phosphate decreased, gamma glutamyl transferase increased, lymphocytes decreased, and hypertension. *For other undesirable effects, please refer to the full prescribing information*. **Preparation**: 200mg x 30's. **Legal Classification:** Part 1, First & Third Schedules Poison. ***Full prescribing information is available upon request.***

API-HK-RZR-24.05

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MAT-HK-2400501-1.0-06/2024

by Dr. Roy Lau

The Role of Matrix Metalloproteases in Tendinopathy and Its Clinical Implications

Tendinopathies are generally referred to as conditions including chronic pain and rupture in tendons. Since inflammatory cells are usually absent in the lesion, tendinopathy has long been recognised as a degenerative condition. Accordingly, anti-inflammatory drugs yielded only modest therapeutic benefits against tendinopathy in previous clinical trials[1]. Remarkably, matrix metalloproteinases (MMP) are potent enzymes that degrade all components of the connective tissue, modify the extracellular matrix (ECM), and mediate the development of painful tendinopathy[2]. Therefore, inhibiting MMP activity to basal levels would potentially reduce excessive tissue degradation and, hence, control the development of tendinopathy.

An Overview of Tendon Disorders

Tendon disorders are one of the most frequent orthopaedic diagnoses, accounting for over 30% of all musculoskeletal consultations. An estimated 30 million cases of tendon and ligament injuries are seen worldwide annually, leading to extensive cost and loss of labour productivity[3]. Although sports injuries contribute to a substantial proportion of tendon disorders, the condition also affects the general population. Essentially, ageing is widely accepted to be associated with the increased prevalence of tendinosis and injury, while degenerative changes in tendons are commonly found in people aged 35 or above[4].

Conventionally, tendinopathy refers to the clinical condition characterised by pain, swelling, functional limitation of the tendon and nearby structures, and subsequently the chronic failure of the healing response process. Of importance is the inflammatory process, which is rare in tendinopathies, but degenerative phenomena are detected in most cases. In fact, tendinopathies are commonly due to overuse conditions, such as in sports and working environments[5]. Interestingly, while exercise is crucial for the rehabilitation in tendinopathies, repetitive loading of a tendon beyond its healing capacity would lead to collagen cross-links failure and, thereafter, collagen fibres start to slide past one another, followed by tissue denaturation[6].

Tendon Structure and Its Remodelling

The key components of the ECM of tendons are the dense, fibrillar network of parallel-aligned collagen fibres, predominantly consisting of type I collagen, proteoglycans and glycoproteins. Notably, the structure and composition are varied within a tendon, particularly at the myotendinous junction and at sites susceptible to compression (**Figure 1**). For instance, upon compressive load or shear, fibrocartilaginous regions, where there is increased expression of type II collagen and aggrecan, would be formed[1].

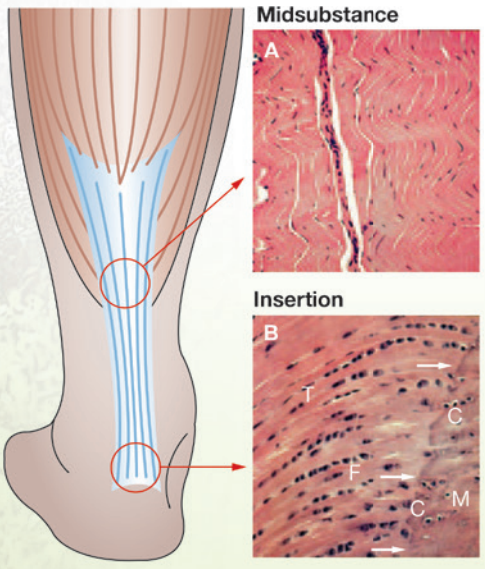


Figure 1. Tendon structure, A) in midsubstance, and B) insertion[1], T: tendon, F: fibrocartilage, C: calcified fibrocartilage, M: mineralised bone

Apart from the structural and compositional variation, tendons are remodelled according to the specific functional demands on them. Highly stressed tendons show increased levels of collagen remodelling than those exposed to less stress. The continual process of tendon matrix remodelling is a constitutive activity affecting proteoglycans in addition to collagen[7], whereas MMPs are reported to be one of the primary mediators.

MMPs and Tendinopathy

MMPs are zinc-dependent endopeptidases that break down collagen in the ECM. There are 4 main groups of MMPs, organised according to the substrate preference of these enzymes. Remarkably, MMP-1, -8, and -13 constitute the group of collagenases which cleave all collagen subtypes, especially types I, II, and III collagen, which confer mechanical strength to tissues. MMP-2 and -9 are gelatinases, which degrade smaller collagen fragments released, as well as cleave denatured collagens and type IV collagen. Stromelysins (MMP-3 and -10) degrade proteoglycans, fibronectin, casein, types III, IV, and V collagen. Moreover, matrilysins (MMP-7) are broad-spectrum proteinases engaged in the activation of the other MMPs[2].

With regard to tendinopathy, the condition typically manifests with the overexpression of fibrillar collagens, disorganisation of collagen fibril orientation, a reduction in network collagen content, and altered fibroblast morphology. Essentially, the increase in fibrillar collagens is accompanied by an increase in the expression of MMP-1, -2, -8, -9, and -13, which may contribute to the development of tears since these MMPs breakdown the primary load-bearing collagen fibres. Furthermore, the increased levels of MMP-2 and -9 may be responsible for the altered fibroblast morphology and inhibition of tendon regeneration, which is the hallmark of tendinopathy[8].

Apart from the pathophysiology of tendinopathy, MMPs play an important role in tendon repair and remodelling. For instance, MMP activity is elevated during the inflammatory phase of healing after acute injuries, whereas the increased MMP activity facilitates the repair and regeneration of damaged ECM[9].

The composition of the ECM of tendons depends on the balance between its formation and degradation, while an excess of MMP activity can lead to progressive degeneration and weakening of the ECM[10]. Therefore, the strict regulation of MMP production and activity is vital for ECM homeostasis.

Therapeutic Potential of MMP Inhibition against Tendinopathy

The regulation of MMP occurs at the levels of gene transcription, pro-MMP activation, and inhibition of active MMPs[11]. Remarkably, therapeutic agents inhibiting active MMPs for controlling tendinopathy have been intensively studied. The most common mechanism of action is binding to the zinc site of the MMP enzyme, thereby blocking its activity.

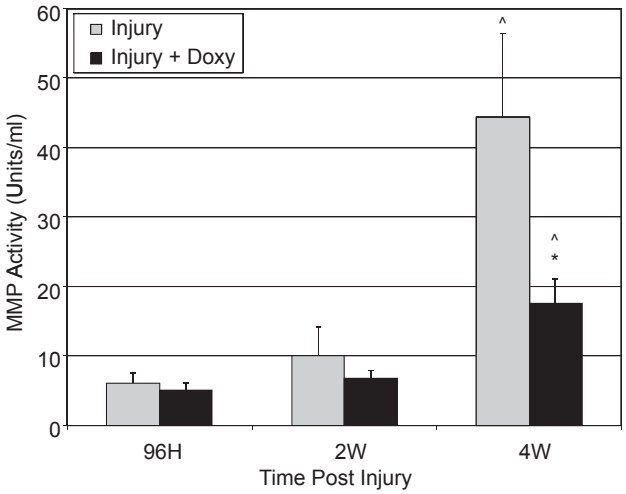


*Figure 2. MMP activity in transected and repaired Achilles tendons[12], *p<0.05 versus injury group, ^p<0.05 versus 96-hour time point, doxy: doxycycline*

Doxycycline is a potent MMP inhibitor, which shows a broad spectrum by inhibiting MMPs -1, -2, -7, -8, -9, -12, and -13. The agent inhibits MMPs not only by zinc-binding but also at the gene expression level and by reducing activation via the inflammatory cascade and through reactive oxygen species (ROS)[11].

Kessler *et al*. (2014) demonstrated in rat Achilles tendon transection models that 4-week oral gavage of doxycycline significantly inhibited MMP activity (**Figure 2**). Also, extended doxycycline administration was associated with improved collagen fibril organisation and enhanced biomechanical properties (**Figure 3A and 3B**)[12]. The results indicated that exposure to doxycycline may improve the repair of Achilles tendon injuries.

Besides doxycycline, the activity of MMPs can be inhibited by tissue inhibitors of metalloproteinases (TIMPs). TIMPs inhibit MMPs by binding to the active site of the MMP catalytic domain. 4 TIMPs have currently been identified, and *in vitro* studies suggest that all 4 TIMPs can inhibit all known MMPs. However, evidence on the clinical performance of TIMPs in controlling tendinopathy is inadequate.

Although the pathophysiology of tendinopathy is yet to be fully understood, the central role of MMPs in tendon homeostasis provides insight into the development of therapeutics against the disease. Remarkably, targeted inhibition of overexpressed MMPs would likely be a promising strategy for countering tendinopathy and improving tendon injuries.

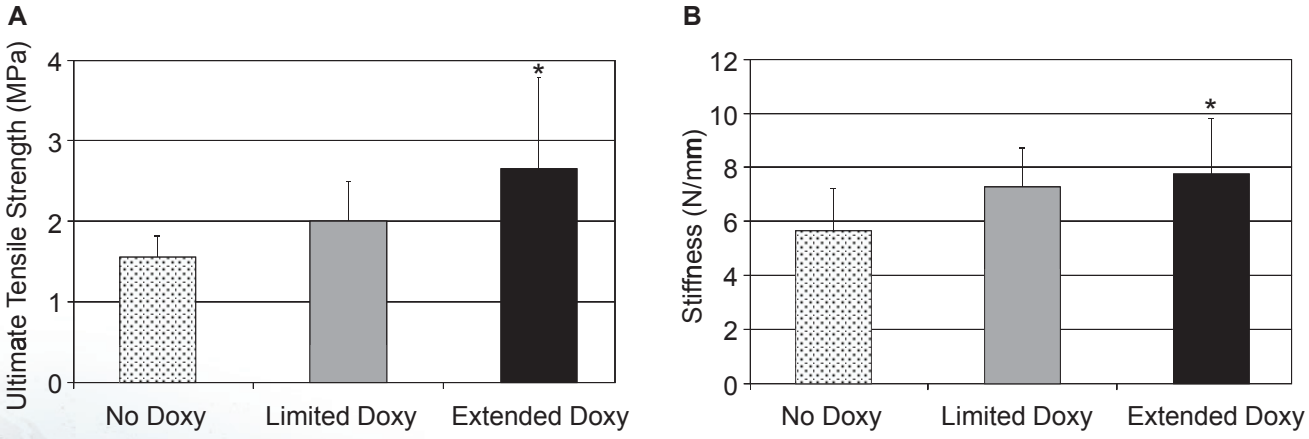
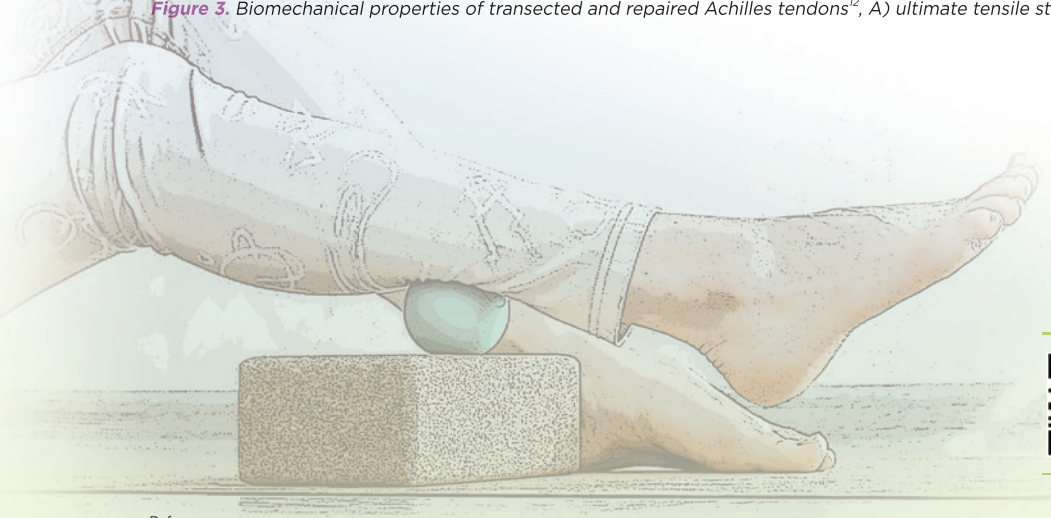


Figure 3. Biomechanical properties of transected and repaired Achilles tendons[12], A) ultimate tensile strength, B) stiffness



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For your triple-class exposed patients with relapsed and refractory (R/R) multiple myeloma (MM)[1,2]

THE POWER TO TRANSFORM IS YOURS[3]

TECVAYLI® has considerable depth and duration of response, improving the chance of long-term survival vs. SoC for patients with R/R MM[4,5]

Upon 23 months mFU, 45.5% of patients on TECVAYLI® achieved ≥CR and the ORR was 63.0%.[4]

Patients on TECVAYLI® demonstrated sustained response with a median DOR of 21.6 months (95% CI, 16.2–NE). The median DOR was extended to 26.7 months (95% CI, 21.6–NE) in patients who achieved ≥CR.[4]

TECVAYLI® is an off-the-shelf immunotherapy that begins with a step-up dosing schedule, followed by weekly subcutaneous administration and a potential reduction to biweekly dosing.[1]

TECVAYLI® has a well-documented and manageable safety profile with few discontinuations (<5%) due to AEs, even after 23 months follow-up.[2,4]

Study design: MajesTEC-1 is a Phase I/II, global, multicentre trial of 165 adult patients with R/R MM that evaluated the efficacy and safety of TECVAYLI®. The primary endpoint was ORR, and secondary endpoints included DOR, TTR, MRD-negative rate, PFS, OS and safety. Results are from patients with a median follow-up time of 23 months.[4]

AE, adverse event; CI, confidence interval; CR, complete response; DOR, duration of response; mFU, median follow-up; MM, multiple myeloma; mPFS, median progression-free survival; MRD, minimal residual disease; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed and refractory; SoC, standard of care; TTR, time to response.

References:
1. TECVAYLI® Hong Kong Prescribing Information P01. 2. Moreau P, et al. N Engl J Med. 2022;387(6):495-505. doi:10.1056/NEJMoa2203478 3. Kumar S, et al. Blood Cancer J. 2022;12(6):98. Published 2022 Jun 29. doi:10.1038/s41408-022-00695-5 4. van de Donk NWCJ, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2–6 June 2023; Chicago, IL, USA & Virtual (Poster no. 8011). 5. Moreau P, et al. Adv Ther. 2023;40(5):2412-2425. doi:10.1007/s12325-023-02480-7

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CP-450306 JUN 2024

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Tel: 2736 1711 Fax: 2736 1926

TECVAYLI® (teclistamab)

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Clinical Trial Snapshot

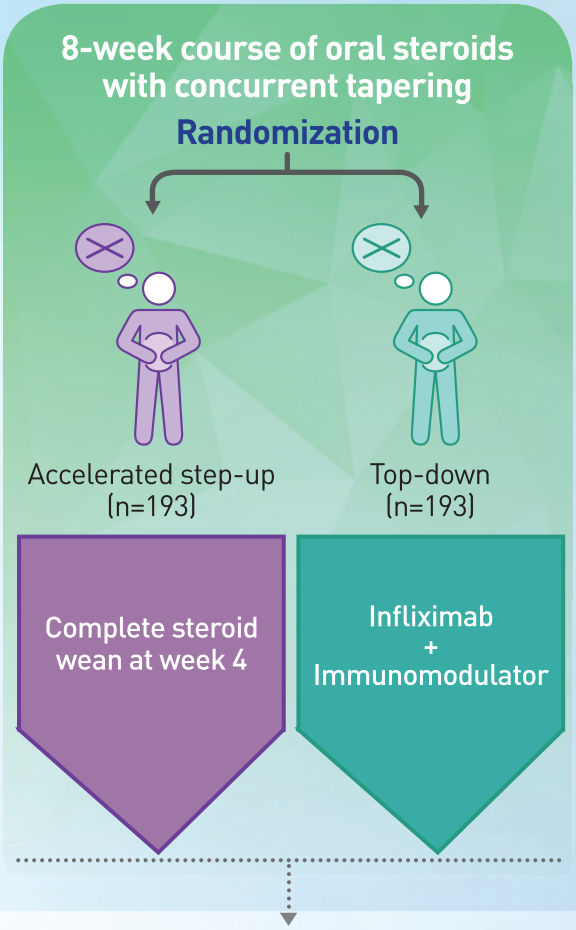
PRedicting Outcomes For Crohn's disease using a moLecular biomarker PROFILE - A multicentre, open-label randomised controlled trial[1]

Objective

To evaluate the use of a putative prognostic biomarker to guide therapy by assessing outcomes in patients with newly diagnosed active Crohn's disease (CD)

Patients

- 16-80 years
- Newly diagnosed active, symptomatic CD (within 6 months; HBI ⩾7; biochemical evidence of active inflammation ; naive to immunomodulator and biologic therapy)



At week 4, 16,32,48

Accelerated step-up

If in remission, continue on current step of treatment

If flare up 1, start steroids and immunomodulator

If flare up 2, start infliximab alongside immunomodulator

Top-down

If in remission, continue infliximab + immunomodulator

If flare up 1, additional course of steroid

If flare up 2, consider nonresponse and trial withdrawal

Primary endpoint

Sustained surgery-free and steroid-free remission

Key secondary endpoints

- Endoscopic remission
- Quality of life
- Number of flares
- Steroid courses
- Crohn's-related hospital admissions and surgeries

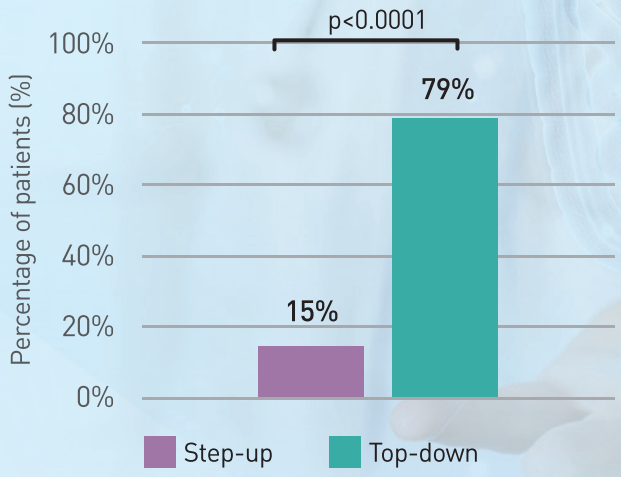
Begin with the Advanced Option From the Top for Better Outcomes for Newly Diagnosed Crohn's Disease

by Benny Chung

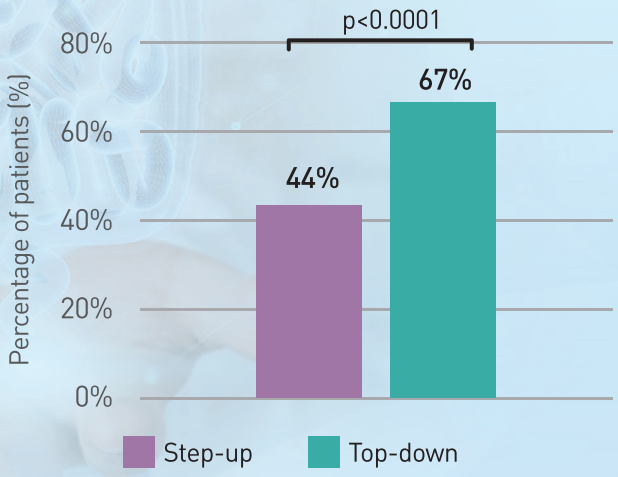
Key Highlights

- The putative **17-gene blood-based biomarker did not show clinical utility** for guiding therapy in CD
- **Remarkably higher remission rates** were seen in patients received **top-down approach**, regardless of the predefined sustained one or endoscopic
- **Top-down approach** showed **greater efficacy in improving quality of life** and **reducing the number of flares requiring treatment escalation**

Sustained steroid-free and surgery-free remission until week 48



Endoscopic remission (absence of ulceration) at week 48



Between-group differences in key secondary endpoints

Quality of life	No. of flares	No. of steroid course	No. of hospitalizations and surgeries
8.54	-1.29	-0.87	-0.12
p<0.0001	p<0.0001	p<0.0001	p<0.0001

- Patients received **top-down approach enjoyed a longer flare-free time** than those with step-up approach did
- The most frequent AE was disease flare, and there were **fewer AEs or SAEs in the topdown group** than in the accelerated step-up group

AE, adverse event; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; SAE, serious adverse event.

Reference: Noor NM, et al; PROFILE Study Group. Lancet Gastroenterol Hepatol. 2024 May;9(5):415-427.

by Eura So

TARGRETIN™

(bexarotene) **MAIN LIFE**

HK Reg. No. HK-68294 (04 Jul, 2024)

Composition:[1]

Targretin™ (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). Targretin™ is available in capsule form containing 75 mg of bexarotene.

Indication:[1]

Targretin™ (bexarotene) capsules is indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

LEQEMBI®

(lecanemab) **EISAI**

HK Reg. No. HK-68289 (03 Jul, 2024) & HK-68290 (03 Jul, 2024)

Composition:[3]

LEQEMBI® is an amyloid beta-directed antibody with the active ingredient lecanemab-irmb. It is administered as an intravenous infusion at a recommended dosage of 10 mg/kg that requires dilution.

Indication:[3]

LEQEMBI® is indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease.

AKEEGA™

(niraparib and abiraterone acetate) **JOHNSON & JOHNSON**

HK Reg. No. HK-68296 (09 Jul, 2024) & HK-68295 (09 Jul, 2024)

Composition:[2]

AKEEGA™ is a combination of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, and abiraterone acetate, a CYP17 (Cytochrome P450 17A1) inhibitor. It is available in 50 mg and 100 mg tablet forms.

Indication:[2]

AKEEGA™ is indicated with prednisone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC).

LITFULO™

(ritlecitinib) **PFIZER**

HK Reg. No. HK-68283 (28 Jun, 2024)

Composition:[4]

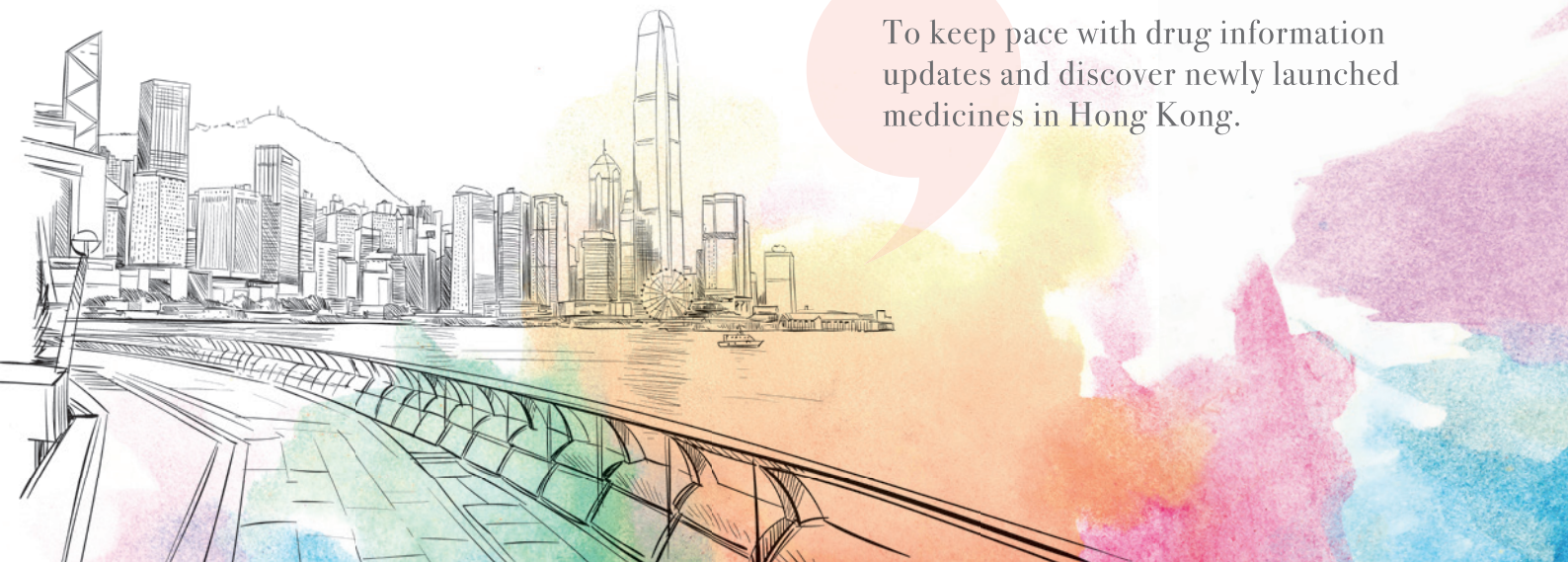
LITFULO™ is a kinase inhibitor available in the form of capsule with 50 mg ritlecitinib.

Indication:[4]

LITFULO™ is indicated for the treatment of severe alopecia areata in adults and adolescents 12 years and older. It is not recommended for use in combination with other JAK (Janus kinase) inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

References

1. TARGRETIN®. HIGHLIGHTS OF PRESCRIBING INFORMATION US 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021055s006lbl.pdf **2.** AKEEGA™. Package Insert 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021055s006lbl.pdf **3.** LEQEMBI®. HIGHLIGHTS OF PRESCRIBING INFORMATION US 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf **4.** LITFULO™. HIGHLIGHTS OF PRESCRIBING INFORMATION US 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215830s000lbl.pdf



One Target, Dual Action, Five Indications

DUPIXENT targets IL-4Ra with dual action on both IL-4 & IL-13 to reduce Type 2 inflammation[1,2]

DUPIXENT - your versatile biologic that targets five conditions[3]

Atopic Dermatitis (AD)

- Moderate-to-severe AD in adults and adolescents ≥12 years old†
- Severe AD in children 6 months to 11 years old†

6+ months

Asthma

- In adults and adolescents ≥12 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation*
- In children 6 to 11 years old as add-on maintenance treatment for severe asthma with Type 2 inflammation^

6+ years

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

- As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP#

18+ years

Newly approved

Prurigo Nodularis (PN)

- Moderate-to-severe PN in adults who are candidates for systemic therapy

18+ years

Newly approved

Eosinophilic Esophagitis (EoE)

- In adults and adolescents ≥12 years old weighing ≥40 kg‡

12+ years

† Candidates for systemic therapy
* Characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.
^ Characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.
# For whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.
‡ Those who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.
Abbreviations: AD=atopic dermatitis; CRSwNP= chronic rhinosinusitis with nasal polyps; EoE= eosinophilic esophagitis; FeNO=fractional exhaled nitric oxide; ICS=inhaled corticosteroids; PN=prurigo nodularis.

References:
1. Guttman-Yassky E, et al. J Allergy Clin Immunol. 2019;143(1):155-172. 2. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15(1):35-50 3.DUPIXENT® Hong Kong Prescribing Information

Presentation: Dupilumab solution for injection in a pre-filled syringe with needle shield. Indications: Atopic Dermatitis (AD): Moderate-to-severe AD in adults and adolescents ≥12 years who are candidates for systemic therapy; severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy. Asthma: In adults and adolescents ≥12 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment. In children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. For 300 mg only – Chronic rhinosinusitis with nasal polyposis (CRSwNP): As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. Prurigo Nodularis (PN): Moderate-to-severe PN in adults who are candidates for systemic therapy. Eosinophilic esophagitis (EoE): In adults and adolescents ≥12 years, weighing ≥40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy. **Dosage & Administration:** Subcutaneous injection. AD adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. AD adolescents (12-17y/o): Body weight <60 kg- initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W. Body weight ≥60 kg- same dosage as adults. AD children (6-11y/o): Body weight 15kg~<60 kg- initial dose of 300 mg on Day 1 follow by 300 mg on Day 15, then 300mg Q4W. Body weight ≥60 kg- same dosage as adults. * The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg~< 60 kg based on physician's assessment. AD children (6 months-5y/o): Body weight 5kg~<15 kg- initial dose of 200 mg, then 200 mg Q4W. Body weight 15kg~<30 kg- initial dose of 300 mg, then 300 mg Q4W. Dupilumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, e.g. face, neck, intertriginous and genital areas. Consider discontinuing treatment in patients who have shown no response after 16 weeks. Asthma adults and adolescents: Initial dose of 400 mg, followed by 200 mg Q2W. For patients with severe asthma and on oral corticosteroids or with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP- initial dose of 600 mg, followed by 300 mg Q2W. Asthma children (6-11y/o): Body weight 15kg~<30 kg- 300 mg Q4W. Body weight 30kg~<60 kg- 200 mg Q2W; or 300 mg Q4W. Body weight ≥60 kg- 200 mg Q2W. For paediatric patients (6-11y/o) with asthma and co-morbid severe atopic dermatitis, as per approved indication, the recommended dose should follow AD children (6-11y/o). Patients receiving concomitant oral corticosteroids may reduce steroid dose gradually once clinical improvement with dupilumab has occurred. The need for continued dupilumab therapy should be considered at least annually as determined by a physician. CRSwNP: Initial dose of 300 mg, followed by 300 mg Q2W. Consider discontinuing treatment in patients who have shown no response after 24 weeks. PN: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W. Dupilumab can be used with or without topical corticosteroids. Consider discontinuing treatment in patients who have shown no response after 24 weeks. EoE: 300 mg QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing <40 kg. Dosing beyond 52 weeks has not been studied. For Missed dose instructions, please refer to the full prescribing information. **Contraindications:** Hypersensitivity to dupilumab or any of the excipients. **Precautions:** Not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm or status asthmaticus. Do not discontinue corticosteroids abruptly upon start of dupilumab. Reduction should be gradual and performed under supervision of a physician; it may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Biomarkers of type 2 inflammation may be suppressed by systemic corticosteroid use. If systemic hypersensitivity reaction occurs, discontinue dupilumab and initiate appropriate therapy. Be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in patients with eosinophilia. Treat pre-existing helminth infections before initiating dupilumab. If patients become infected while receiving dupilumab and do not respond to anti-helminth treatment, discontinue dupilumab until infection resolves. Cases of enterobiasis were reported in children 6 to 11 years old in the paediatric asthma development program. Advise patients to promptly report new onset or worsening eye symptoms. Patients who develop conjunctivitis, dry eye and keratitis that does not resolve following standard treatment should undergo ophthalmological examination. Sudden changes in vision or significant eye pain that does not settle warrant urgent review. Patients with comorbid asthma should not adjust or stop asthma treatments without consultation with physicians. Carefully monitor patients after discontinuation of dupilumab. Avoid using live and live attenuated vaccines concurrently with dupilumab. Patients should be brought up to date with immunisations before starting dupilumab. **Drug Interactions:** Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed. Patients receiving dupilumab may receive concurrent inactivated or non-live vaccinations. **Pregnancy and lactation:** Should be used during pregnancy only if potential benefit justifies potential risk to foetus. Unknown whether dupilumab is excreted in human milk or absorbed systemically after ingestion. Decision must be made whether to discontinue breast-feeding or dupilumab taking into account benefit of breast feeding for the child and benefit of therapy for the woman. **Undesirable effects:** Most common adverse reactions reported- injection site reactions, conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, eosinophilia and injection site bruising. Safety profile observed in adolescents and children 6 months to 11 years old consistent with that seen in adults. For other undesirable effects, please refer to the full prescribing information. **Preparation:** 2 x 300mg/2ml in pre-filled syringe with needle shield, 2 x 200mg/1.14ml in pre-filled syringe with needle shield. **Legal Classification:** Part 1, First & Third Schedules Poison **Full prescribing information is available upon request.**

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Generally well tolerated with transient adverse events[9,10]

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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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