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The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong

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INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Education & Practice
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- OTC & Health
- Pharmaceutical Techniques & Technology
- Medication Safety
- Herbal Medicines & Nutraceuticals
- Society Activities
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Comments on any aspects of the profession are also welcome as Letter to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

Return of the Hong Kong Pharmacy Conference

The Hong Kong Pharmacy Conference, which was stopped after the one in 2019 due to the outbreak of COVID-19, was recently held successfully. COVID-19 has had a significant impact on the healthcare systems worldwide, including Hong Kong. The pandemic has also led to changes in the way healthcare services are provided and has created new opportunities in various aspects of healthcare. The resumption of the conference is an important milestone for the pharmacy profession in Hong Kong, as it provides a platform to share the experiences and lessons learnt from the pandemic and to discuss the challenges that the profession is facing under the "new normal". The success of the conference is a testament to the resilience and commitment of the pharmacy community in Hong Kong to advancing the profession and improving patient care.

IU, Pui Chinga and CHONG, Donald Wing Kit wrote an article on "The trend to watch – real-world data & real-world evidence" on page 7. This article provided an overview of real-world data and real-world evidence and its applications. Real world data is becoming increasingly important in pharmacy as it provides valuable insights into the safety and effectiveness of drugs and other healthcare interventions in real-world settings. Pharmacists can play a significant role in the era of real-world data and real-world evidence. Pharmacists can leverage their expertise in medication management to help identify and collect relevant real-world data and real-world evidence, as well as analyze it to generate insights that can improve patient care. In addition, pharmacists can work with other healthcare providers to identify gaps in patient care and develop interventions to address them.

ZHENG, Sin-Man Michelle wrote an article on "Overview of the drug therapy of psoriasis" on page 16. Psoriasis is a chronic autoimmune disorder that affects the skin. It can cause a range of physical and emotional distress and has a significant impact on quality of life on patients with psoriasis. Although psoriasis cannot be cured, it can be managed with a variety of treatments. This article provided an overview of treatment therapies of psoriasis that can help to reduce symptoms and improve quality of life for patients with psoriasis.

I hope that you enjoy this issue. As always, your suggestions on any part of the Journal is valuable and can send the comments to me or other members of the Editorial Committee.

May PS Lam
Editor-in-Chief
02 May 2023

Prepared by Branson Fok and Chloe Ip

Aspirin Non-Inferior to Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture

Date: Jan 19, 2023

Venous thromboembolism is a potentially fatal complication after orthopedic trauma. Clinical guidelines recommend low-molecular-weight heparin (LMWH) as thromboprophylaxis after a fracture while recent trials and meta-analyses suggested aspirin as an effective and safer alternative. Limited studies with head-to-head comparisons were however found.

In this pragmatic, multicenter, randomized, noninferiority PREVENT CLOT trial, the effectiveness and safety of thromboprophylaxis with aspirin were compared to LMWH in adults with an extremity fracture treated surgically or any pelvic or acetabular fracture treated surgically or nonsurgically. At 21 trauma centers located in the United States and Canada, a total of 12,211 patients were randomly assigned to receive 81 mg of oral aspirin (6101 patients) or 30 mg of subcutaneous enoxaparin (6110 patients), both groups received treatment twice daily while hospitalized. After hospital discharge, patients continued to receive thromboprophylaxis according to the clinical protocols of each hospital. The primary outcome was death from any cause at 90 days. Secondary outcomes included nonfatal pulmonary embolism, deep-vein thrombosis, and bleeding complications.

Patients received a mean of 8.8±10.6 in-hospital thromboprophylaxis doses and were prescribed a median 21-day supply of thromboprophylaxis at discharge. Death occurred in 47 (0.78%) and 45 (0.73%) patients in the aspirin and LMWH groups, respectively (difference, 0.05 percentage points; 96.2% confidence interval [CI], -0.27 to 0.38; P<0.001 for a noninferiority margin of 0.75 percentage points). Deep-vein thrombosis occurred in 2.51% and 1.71% of patients in the aspirin and LMWH groups, respectively (difference, 0.80 percentage points; 95% CI, 0.28 to 1.31). The incidence of pulmonary embolism, bleeding complications, and other serious adverse events were similar in the two groups.

The trial concluded that in patients with extremity fractures who had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin was noninferior to low-molecular-weight heparin in preventing death and was associated with a lower incidence of deep-vein thrombosis and pulmonary embolism and a lower 90-day mortality rate.

Source: www.nejm.org

Baxdrostat Demonstrated Substantial Reductions in Systolic and Diastolic Blood Pressure in Patients with Treatment-Resistant Hypertension

Date: Feb 2, 2023

Treatment-resistant hypertension is defined as elevated blood pressure despite of concurrent use of at least three antihypertensive drugs of different classes, including a diuretic. This condition is affecting approximately 10% of patients with hypertension in the United States (10 to 12 million people) and has a substantially increased risk of cardiovascular and renal adverse events. Pre-clinical and phase 1 studies on baxdrostat have shown high selectivity (selectivity ratio, 100:1) for aldosterone synthase inhibition, however, data on its efficacy and safety for patient use is warranted.

In this multicenter, placebo-controlled, randomized trial, patients who had treatment-resistant hypertension with a blood pressure of 130/80 mm Hg or higher and were receiving stable doses of at least three antihypertensive agents including a diuretic, were enrolled to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks or placebo. The primary endpoint was the change in systolic blood pressure from baseline to week 12 in each baxdrostat group as compared with the placebo group.

A total of 248 patients received either once-daily baxdrostat at a dose of 0.5 mg (65 patients), 1 mg (60 patients), or 2 mg (56 patients), or placebo (67 patients) completed the 12-week treatment period. At week 12, baxdrostat was associated with dose-dependent changes in systolic blood pressure of -20.3 mm Hg in the 2 mg group, -17.5 mm Hg in the 1 mg group, -12.1 mm Hg in the 0.5 mg group and -9.4 mm Hg in the placebo group. Significant changes in systolic blood pressure were observed between the 2 mg group and the placebo group (-11.0 mm Hg, 95% confidence interval [CI], -16.4 to -5.5; P<0.001) as well as between the 1 mg group and the placebo group (-8.1 mm Hg, 95% CI, -13.5 to -2.8; P=0.003). No deaths occurred during the trial, and baxdrostat had a generally tolerable side-effect profile. There were no instances of adrenocortical insufficiency.

In conclusion, aldosterone synthase inhibition with baxdrostat is effective for substantial reductions in systolic and diastolic blood pressure in patients with treatment-resistant hypertension.

Source: www.nejm.org

Bempedoic Acid Lowers the Incidence of Major Adverse Cardiovascular Events in Statin-Intolerant Patients

Date: Mar 4, 2023

Seven to twenty-nine percent of patients reported adverse musculoskeletal effects which lead to their avoidance to statins or intolerance to guideline-recommended doses. Bempedoic acid, an ATP citrate lyase inhibitor with similar mechanism to statins, increases clearance of LDL cholesterol from the circulation and is associated with a lower incidence of musculoskeletal adverse events. However, its effect on cardiovascular outcomes remains uncertain.

In this double-blind, randomized, placebo-controlled trial, patients who were unable or unwilling to take statins due to unacceptable adverse effects and had, or were at high risk for cardiovascular disease, were recruited across 1250 sites in 32 countries. A total of 13,970 patients were randomly assigned in a 1:1 ratio to receive oral bempedoic acid, 180 mg daily (n = 6992), or a matching placebo (n = 6978). The primary endpoint was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Patients were followed for a median duration of 40.6 months.

The mean LDL cholesterol level for the participants in the both groups was 139.0 mg per deciliter at baseline. After 6 months, the level was 107.0 mg per deciliter with bempedoic acid compared to 136.0 mg per deciliter with placebo, with a difference of 29.2 mg per deciliter (0.76 mmol/L). The observed difference in the percent reductions was 21.1 percentage points (95% confidence interval [CI], 20.3 to 21.9) in favour of bempedoic acid. The incidence of a primary endpoint event was significantly lower in the bempedoic acid group than in the placebo group (819 patients [11.7%] vs 927 [13.3%]; hazard ratio, 0.87; 95% confidence interval [CI]. 0.79 to 0.96; P=0.004). The incidence of a composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction were also significantly lower with bempedoic acid than with placebo. The bempedoic acid group had however a higher incidence of gout, cholelithiasis, elevated hepatic enzymes, renal impairment, and hyperuricemia.

The study concluded that treatment with bempedoic acid among statin-intolerant patients was associated with a lower risk of major adverse cardiovascular events including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

Source: www.nejm.org

Noninferiority of Bedaquiline–Linezolid Regimen to Standard Treatment for Rifampin-Susceptible Tuberculosis

Date: Mar 09, 2023

A 24-week rifampin-based regimen is a common treatment practice for rifampin-susceptible pulmonary tuberculosis. Long-term adherence issue is a major concern that warrants investigation of new treatment approaches with shorter duration and compatible effectiveness.

In this phase 2 to 3, international, adaptive, randomized, open-label, noninferiority TRUNCATE-TB trial, patients with rifampin-susceptible tuberculosis were randomly assigned to receive either the standard treatment or a trial 8-week regimen. The trial regimen included four strategy groups: high dose rifampin-linezolid, high dose rifampin-clofazimine, rifapentine-linezolid, and bedaquiline-linezolid, each in combination with isoniazid, pyrazinamide, and ethambutol or levofloxacin for the rifapentine–linezolid group. After the 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse were done. The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. Noninferiority was assessed in high-dose rifampin–linezolid and bedaquiline–linezolid groups with complete enrollment and the margin was 12 percentage points.

A total of 674 participants with an age range of 18-65 years were enrolled. The strategy with an initial bedaquiline-linezolid regimen was noninferior to the standard treatment, in which the primary-outcome event occurred in 11 of the 189 participants (5.8%) (adjusted difference, 0.8 percentage points; 97.5% CI, −3.4 to 5.1; noninferiority met) as compared with 7 of the 181 participants (3.9%) in the standard-treatment group. The mean total duration of the bedaquiline–linezolid strategy group and the standard treatment group were 85 days and 180 days respectively. The incidence of grade 3 or 4 adverse events, serious adverse events, and respiratory disability did not differ significantly between the standard-treatment group and the two strategy groups.

A strategy involving initial treatment with a bedaquiline–linezolid regimen was noninferior to standard treatment for tuberculosis concerning clinical outcomes, which was also associated with a shorter total duration of treatment and with no apparent safety concerns.

Source: www.nejm.org

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Pharmaceutical Studies

MSc Clinical Pharmacy*

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Programme Features:

- Updated specialist modules
- Realistic project workload for timely completion
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- High and timely completion rate

Entry Requirements:

A minimum of lower second class honours degree in pharmacy (or equivalent) and registration as a pharmacist in Hong Kong.

BPharm graduates from countries that do not normally award honours may also apply, provided they are registered as a pharmacist in Hong Kong. The programme is open to both hospital and community pharmacists.

University of Sunderland

Application Code: 2150-HS073A
Programme Code: HS073A

Application Deadline: 30 June 2023

Enquiries
3762 0096
lily.twl.chan@hkuspace.hku.hk

* This is an exempted course under the Non-local Higher and Professional Education (Regulation) Ordinance. It is a matter of discretion for individual employers to recognise any qualification to which this course may lead.
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Professional Diploma in Marketing for Pharmaceutical Industries

The objectives of the programme are to equip the practitioners of pharmaceutical industry or medical devices business or those who intend to develop their career in marketing in these two industries with solid knowledge and practical skills in marketing, selling, tender planning and pitching, market knowledge and the latest trends in product development. The graduates of this programme will be able to develop marketing strategies, prepare tender proposal and manage business pitching abiding by regulations and code of practice of the industry concerned.

Programme Features:

- Students can choose to focus on either the pharmaceutical market / the medical device business
- Emphasis on practicality and the curriculum responds to the business needs of the pharmaceutical and medical device industries
- Interactive learning with lots of case studies, discussion and sharing by guest speakers
- Experienced and well-qualified lecturers
- Strong connection with the industries

Entry Requirements:

Applicants should hold:

- A Diploma/ Advanced Diploma awarded by a recognized institution; or
- A Professional Certificate in Marketing awarded within the HKU system through HKU SPACE or equivalent.

Applicants with a science background are preferred.
Applicants with other equivalent qualifications and relevant work experience will be considered on individual merit.

資歷架構 Qualifications Framework
Level 4
Registration Number:19/001296/L4
Valid From:01 Feb 2020 - on-going

Application Code: 2135-MK075A
Programme Code: MK075A

Application Deadline: 10 June 2023

Enquiries
2867 8499 / 3762 0096
pharma.mkt@hkuspace.hku.hk

Certificate for Module (Medical Operations in Pharmaceutical Industry)

This programme aims at introducing medical operations in the pharmaceutical industry to students who are interested. These operations include regulatory affairs, medical affairs, medical science liaison, clinical trial, quality assurance, and pharmacovigilance.

Programme Features:

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- Emphasis on current practices of the departments with medical operations in the pharmaceutical industry
- Interactive learning with lots of case studies, discussion and sharing by guest speakers
- Experienced and well-qualified lecturers
- Strong connection with the industries

Entry Requirements:

Applicants shall have attained:

- A Certificate in a related discipline; or
- Level 2 or above in five subjects including English Language in the HKDSE Examination; or
- Level 2 / Grade E or above in English Language and four other subjects in Grade E or above in the HKCEE or equivalent.

Applicants who hold other qualifications, aged 21 or above and have relevant work experience will be considered on an individual basis.

資歷架構 Qualifications Framework
Level 3
Registration Number:19/001254/L3
Valid From:01 Nov 2019 - on-going

Application Code: 2135-HS173A
Programme Code: HS173A

Application Deadline: 28 June 2023

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The Trend to Watch – Real-World Data & Real-World Evidence

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ABSTRACT

With the advancement in data technology, the use of real-world data (RWD) is becoming a common approach in healthcare research. The potential of real-world evidence (RWE) in complementing randomized clinical trials (RCTs) has been acknowledged by regulatory authorities such as FDA and EMA. In near future, RWD/RWE will play a larger role in supporting regulatory decisions, such as drug approvals and expansion of indications. This article aims to provide pharmacists with an overview of RWD/RWE in terms of its strength and pitfalls. There will also be elaborations on the application possibilities of RWD/RWE in the whole drug product lifecycle, and the current status of real-world studies in Hong Kong. The integral role of pharmacists in understanding, communicating, and generating real-world data will also be discussed.

Keywords: *Real-world Data, Real-world Evidence, Randomized Controlled Trials (RCTs), External Validity, Internal Validity*

INTRODUCTION

Stakeholders in the healthcare ecosystem are always concerned about the cost and time it takes for new medical innovations to gain regulatory approval and market recognition. Over the decades, the magnitude of increase in drug development cost is in spiralling scale; with cost doubling every 9 years.[1, 2] A median of 8 years (range 5-20 years) is required to move a new drug entity from lab bench to bedside, with 6-7 years spent on clinical trials.[3] Regulatory agencies have been using randomized clinical trials (RCTs) as the benchmarking standard for market approval. However, RCTs are expensive, time-consuming, and are not fault-free experiment designs. Scholars and scientists are looking for newer research practices and ideas that could provide complementary evidence to RCTs.

DEFINITION OF REAL-WORLD DATA (RWD) AND REAL-WORLD EVIDENCE (RWE)

Studies derived from real-world data (RWD) are gaining the attention of healthcare stakeholders. They could aid in the safety and efficacy proof of medical interventions that were conventionally dominated by RCTs. "RWD" is not a new term; early traces of RWD are seen way back in literature from the 1980s.[4, 5] However, there is no consensus on the definition of RWD, which prompted The U.S. Food and Drug Association (U.S. FDA) to put forward a definition, after recognizing its potential value in 2018.[6] RWD is defined as "data related to patient health status or delivery of healthcare", excluding those collected from RCTs. The evidence of potential benefits and risks of medical interventions derived from the evaluation of RWD is defined as real-world evidence (RWE).

FEATURES OF RWD

While RWD is often understood as a type of healthcare big data, they are not synonyms. The definition of RWD does not include a criterion for data size.[7] However, the astonishing development speed of big data technology has potentiated RWD to function as a promising source of information to understand our health. Useful RWD generally processes the characteristic of big data, namely the 5Vs: "Volume", "Variety", "Velocity", "Value" and "Veracity".[7, 8]

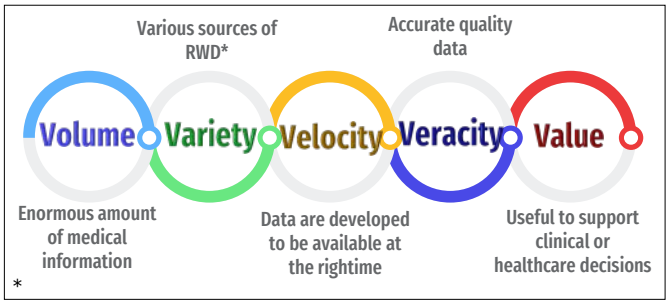

Figure 1*: 5Vs of RWD/ RWE*

The sources of RWD include, but are not limited to: electronic health records (eHRs); health financial claims and billings records; disease registries (databases storing patients' diagnoses); patient-generated data (such as blood glucose monitoring data in ambulatory settings); and data generated from medical devices (such as mobile wearable biosensors).[6]

THE TREND OF RWD AND HOW IS IT RELATED TO PHARMACY PRACTICE?

The application of RWD has been mainly on pharmacovigilance and post-marketing drug safety surveillance. In the last few years, regulatory agencies worldwide are opening their doors to use RWE for approval of pharmaceutical products and medical devices. The U.S. FDA was one of the first agencies to acknowledge RWD's importance. In 2016, the "21st Century Cures Act" was signed into law in the U.S., which aimed to accelerate the process of drug development.[6] Under the provision of the Cures Act, U.S. FDA was called to develop a framework for RWD/RWE. The framework was issued two years later and provided guidance on the role and requirement of RWD/RWE in the approval of new drug indications and in supporting post-approval studies.[9] The European Medicine Agency (EMA) also announced its vision for enabling RWD/RWE to be used in regulatory decision-making by 2025 in the 2020 strategic document, "Regulatory Science Strategy to 2025".[10] In 2021, EMA issued the "Regulatory Science Research Needs Initiatives" which identified 15 RWD/RWE related topics in need of further research to address the current knowledge gap.[11]

The worldwide effort to promote RWD/RWE is expected to impact the current process of drug approval, reimbursement, price negotiation, and also patient-care decision in near future.[12, 13] In view of the transforming landscape of RWD, it is important for us, pharmacists, to have an overview of RWD, to: 1) understand more about its expanded applications in global and local domains, and 2) be able to evaluate the evidence derived from RWD for clinical and regulatory decisions.

CLARIFICATIONS ON SOURCES OF RWD & METHODOLOGIES OF RWE

Among the spectrum of potential RWD sources, one common misconception is that RWD only refers to retrospective data coming from routine healthcare databases. Routine healthcare data such as claims, electronic health records, and pharmacy retail records, are usually not developed with research intention. However, healthcare data could be collected actively, prospectively and under a pre-defined protocol to fulfil specific research purposes. These include well-designed disease registries and patient-generated data. While different types of RWD could come with specific advantages and disadvantages (illustrated in **Table 1**), their shared characteristic is that they are health status-related data that are generated outside clinical trial setting.[14]

Another commonly confusing concept to be cleared up is the two related terms, RWD and RWE. RWE is the evidence generated from the analysis of RWD. When compared to RCT, the methodologies used to generate scientific and clinical evidence from RWD are far more complex and have greater variability. RWE studies are often described as observational studies, but they are not equivalent. Non-interventional observation study designs, often use RWD as their main source of data. These include cohort studies which could be prospective or retrospective in nature, retrospective case-control studies, and cross-sectional studies.[14]

On the other hand, interventional studies such as pragmatic trials (or pragmatic randomized control trials) (PCT) could also be used to generate RWE. The aim of RCTs can be described by a continuum between the two extremes: explanatory and pragmatic.[15, 16] Traditional RCTs are more of an explanatory purpose which the main focus is to explore the effect of interventions; while PCTs aim to inform clinical and policy decisions.[17, 18] Both RCT and PCT involve randomization for control to avoid potential bias. However, the level of randomization is lower in PCT which is only at cluster level (e.g. hospital level) but not individual level. The inclusion and exclusion criteria and the requirement for intervention adherence are also less stringent when compared to RCT. In this way, PCT could reflect effectiveness in usual care.

HOW RWE STUDIES COMPLEMENT RCTs

Large sample size

With the advancement of big data technology, RWD is able to provide a large heterogeneous sample in a much quicker and cheaper approach than RCT, and can provide opportunities in the study of rare diseases. Traditional RCTs on rare diseases are challenging in terms of patient recruitment and burden to test and measure outcomes.[26] Currently, only 5% of rare disease have approved treatment.[27] Hence, RWE studies may be one of the few feasible approaches to facilitate the evaluation of potential orphan treatments for rare diseases.

Efficacy and effectiveness

While RCTs are regarded as the gold standard for evaluating efficacy of interventions, RWE could provide supplementary evidence in effectiveness of the treatment.[28, 29] In a general context, "efficacy" and "effectiveness" could be used mutually and reciprocally. However, in research, interventions are said to be "efficacious" if the desired effect could be demonstrated under well-defined and ideal circumstances. On the other hand, effective interventions are those which have capacity to produce expected performance in real-world practice. When compares to RCT, treatment patterns and

Table 1: Source of RWD			
Source of RWD[19]	**Examples**	**Advantages**	**Disadvantage**
Claims[20]	• Medical insurance claims • Health Financial claims • Drug claims	• Applicable for countries/ regions implemented national medical insurance schemes • Cost-effective method of collection of readily available data • Patients with specific medical conditions are easily identified	• Validity of record may be limited as data are recorded for reimbursement purpose • Data shared between different agencies, some data details (e.g. adverse events, radiology and laboratory test results) may not be captured • Incomplete information regarding some sensitive diagnoses and medication dosages
Registries[21]	• Disease registry (storage of patient diagnosis) • Product (drug and devices) registries (e.g. Pregnancy exposure registries) • Procedures or health service registries	• Well-designed registries could collect comprehensive information such as patient demographics, risk factors contributing to disease, disease progression, relapsing, remitting, and severity • Provide a large sample size of longitudinal data • Access long-term effectiveness and safety of interventions	• Prone to selection bias (most registries are voluntary, only those willing to participate are recruited) • Difficult to conduct data verification • Underestimation of events due to loss to follow-up, loose monitoring of patient's condition • Duplicate records due to anonymous data collection • Absent of control group
Clinical data[22]	• Electronic health records (eHRs) which include laboratory tests • Hospital billing data	• Reduce the cost and effort of data collection • Contains representable data from targeted group of patients • Provides comprehensive longitudinal data	• Statistical adjustment might be needed when conducting multiple hypothesis study, which may result in biased findings • eHR is not built for research purposes but is intended for clinical use, extensive data processing procedure may be required for data analysis • only capture patients' activities who utilize hospital services
Pharmacy/Retail record[23, 24]	• Drug sales data • Prescription data	• Allow the assessment of continuity of care for patients when integrated with eHR	• Non-unified standard of pharmacy data makes it difficult for data analysis
Patient generated data[25]	• Glucose monitoring data in ambulatory settings • Data generated from medical devices such as mobile wearable biosensors (heart rate, blood pressure etc) • Social media • Patient advocacy organization	• Suitable for the study related to non-prescription medications • Suitable for chronic disease studies	• Selection bias may arise as people with advanced age, lower education level, lower technology and health literacy may have lower usability

therapeutic outcomes involved in RWE studies are more complex. RWD provides data for evaluation of different treatment options which have not been compared head-to-head in RCT studies.[30] In addition, RWD studies could also aid with the assessment on epidemiology, treatment adherence and persistence, prescribing patterns and health resources cost-effectiveness.[31]

External validity and internal validity

RWE studies offer the strength of external validity. External validity, also known as generalizability, is the extent of applying the conclusion of the study on different patients, treatments, or other settings and circumstances. The setting of RCTs focuses on internal validity and is deemed to sacrifice its generalizability in real-world. Internal validity refers to the degree of confidence for the observed causal relationship is representing the truth in the group of population under study, but not due to systemic errors or random errors.[29] The imposition of inclusion and exclusion criteria in RCT study protocol is a standard practice. The advantages of this practice include increasing the reliability and reproducibility of study outcomes in answering the research question; minimizing the probability of recruiting patients which may interfere with study results; and lessening risk of posing adverse events to vulnerable patients.[26] By adhering to the selection criteria in study protocols, RCTs could maximize the internal validity of the study.[29, 32] However, individuals of extreme ages, multi-comorbidity, polypharmacy, and patients with difficulties complying with study protocols, are often underrepresented in RCTs.[29] Although good internal validity is the prerequisite of external validity,[33] RCTs with narrower population selection increase the difficulty of applying the results to routine clinical practice.

On the other hand, the sources of data from RWE usually contain a larger pool of heterogenous samples than RCTs. Treatment outcomes from RCT-excluded patients (such as elderly patients and renally repaired patients) could be retrieved and analysed in RWE studies.[31, 34] RWE can supplement RCT by providing a greater external validity from their findings.

An example showing the gap between RCTs sample population and real clinical practice population was illustrated by Kennedy-Martin et.al[35] in a literature review on RCTs to examine their external validity . The review included 52 RCTs on oncology, mental health and cardiology. The review evaluated the RCTs by two methods: (1) comparing the demographics of sample population in RCTs statistically with patients in routine clinical practice, or (2) determined the ineligibility rates of real-world patients that could not satisfy the inclusion criteria of the RCTs. It was found that real-world patients often had higher risk characteristic when compared to RCTs samples. These risk factors included older age, worse disease prognosis, more co-morbidities and less likely to receive guideline-recommended therapies. In all three studied disease areas, the majority of the RCTs reviewed had a real-world ineligibility rate greater than 50% (44.4% for cardiology, 88.9% for mental health, and 66.7% for oncology). The author suggested that more restrictive criteria used in sample selection (for higher internal validity) signifies greater difficulty for the RCT to provide an accurate perspective of drug efficacy and safety in real-world clinical practice.

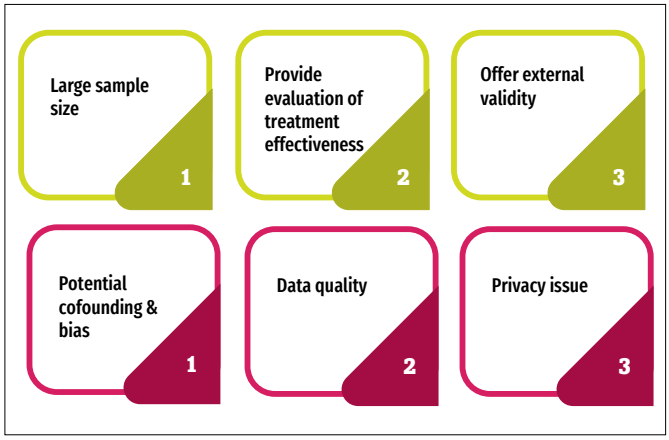

***Figure 2**: Strength and Pitfalls of RWD/RWE*

POTENTIAL IMPEDIMENTS OF RWE

While RWE gives higher generalizability than RCT, there are intrinsic limitations constraining its acceptance from some researchers. In the evidence hierarchy of evidence-based medicine, RCT is ranked as the most scientific vigorous research method among single study settings. The robustness of RCTs attributes to the randomization process which reduces between-group-comparability. The baseline demographics between the treatment group and control group are balanced, which lowers selection bias and minimizes cofounding factors when identifying cause-to-outcome relationships.[28] For RWE studies, many pitfalls need to be carefully watched over when expanding its use. Despite that, many of these limitations are well-recognized by researchers. Different measures have been taken to optimise the potential uses of RWD sources and RWE studies.

Cofounding & bias

The lack of randomization increases the risk of cofounding and bias in RWE studies. Cofounding refers to some unobservable or unmeasured variables which could affect the cause-effect analysis of a study.[31] Major bias in RWE studies includes selection and information bias. Selection bias arise when there are factors during the patient selection process that could influence the representativeness of the intended population to be studied. For example, data from healthier and younger patients tend to be more available from insurance claims.[36] Information bias includes recall bias, and reporting bias which may be prominent in patient-generated data.

To minimize bias and adjust for cofounding factors, strategies depending on the type of cofounders (measured confounders, unmeasured but measurable cofounders, and unmeasurable cofounders) can be utilized.[37] For measured cofounders, statistical methodologies such as restriction and stratification of types of patients, matching of controls, and propensity scores are used.[38] In particular, propensity score is a popular statistical tool in observation studies which could be used to adjust for the treatment effect. This is done by calculating the probability of patients receiving the treatment option based on different measured factors (e.g. age and sex).[39] For accounting unmeasured but detectable cofounders, approaches such adjustment using external data and proxy measurement could be employed. For example, Danish National patient registry, diagnosis of chronic obstructive lung disease (COPD) is used as a proxy marker of previous smoking history.[37] To address unmeasurable cofounding factors, some studies may be able to use self-controlled designs, and sensitivity analysis to ensure the robustness of the assessment. Instrumental variables are also a potential way to control cofounding. Instrument variables are variables which covary with the predictor variables but have no effects on the dependent variables. A real-world study aiming to access the effectiveness of nonsteroidal anti-inflammatory drug (NSAIDS) on the treatment of patent ductus arteriosus (PDA) in preterm Infants utilized instrumental variables. The instrument used was institutional variation in NSAIDs prescribing frequency. This instrument variable is incorporated into the analysis to illustrate the effect of the predictor variable (NSAIDs exposure) on the dependent variable (PDA closure).[40]

Missing data and lack of data consistency

Many RWDs, such as eHRs, are considered as refined and structured databases and have great potential to support RWE studies. However, eHRs are primarily built for routine clinical practice and are not intended for research studies. When data are extracted from eHRs for research, their unique complexity and significant inaccuracies become visualized to the researchers. For example, manual entering of eHR often embedded with various transcription errors which are difficult to trace. In addition, non-numerical characters, free texts, unstandardized abbreviations are commonly found in

eHRs.[41] Thus, direct data analysis is often impossible, as researchers need to go back to review the original patient chart and make data modifications. Some patient demographics such as height and weight may not be routinely measured or may rely on patient reported value. Furthermore, the change of these demographics over the treatment period may not be recorded, which may become an unaccounted covariate or cofounder in the study.[41]

Different initiatives have been proposed to leverage data standardisation from RWD. To facilitate the electronic exchange of clinical information, electronic documentation and entry should use consistent terminologies. For example, Systematized Nomenclature of Medicine, Clinical Terms (SNOMED-CT) and International Classification of Diseases (ICD) are universal languages of healthcare that could be adopted.[42] Computer translation programs is a solution to tackle unstandardized images, signals or any other form of clinical data.[43] An international collaborative, the Observational Health Data Sciences and Informatics (OHDSI), was initiated to explore different data models to transform medical data into a consistent manner for research purpose, and allows researchers to utilize its open network as a data holder, as every element in the original data will be mapped to common vocabularies within the data model. This international effort is important in facilitating world-wide multicentred studies and expanding the feasibility of RWE studies.[44]

REGULATORY & PRIVACY ISSUES

There are three aspects in the main footing of regulatory bodies on RWE regulation: (1) the establishment of regulatory frameworks to outline the use of RWE in the product lifecycle; (2) creating consensus and guidance for standardization of RWE study designs and data management; (3) addressing data privacy issues relating to RWD.[45, 46]

Regulatory frameworks for RWE

A clear regulatory framework for RWE is vital to expand the usage of RWE usage in product life-cycle. The FDA RWE framework was first released in 2018 as mandated under 21st Century Cures Act. In October 2022, an official guidance on submitting documents using RWD to FDA for drug and biological products was issued. The final guidance included a list of proposed purposes for RWD/RWE for the support of changes in indication; changes in dose, regimen and route of administration; adding new patient population; adding comparative effectiveness information and safety information, etc.[47] Other regulatory agencies, such as European Medicines Agency (EMA) and the European Commission, Medicine and Healthcare Products Regulatory Agency of United Kingdom, National Medical Products Administration (NMPA) in China, the Taiwan Food and Drugs Administration (TFDA) have either released similar guidance documents or are in the process of generating one. Other countries such as Singapore, South Korea, Australia and New Zealand have been showing increasing interest in broadening the use of RWE in regulatory decision making.[45]

Guidelines for standardization of RWE study designs and data management

The quality of RWD database and RWE study design are also concerns of regulatory agencies. When evaluating evidence derived from RWD, there should be no "one size fits all" approach.[48] However, general requirements still hold, such as whether the RWD is fit for the study purpose, and the adequacy of scientific evidence provided by the RWE study design.[45] The FDA introduced the Advanced RWE program in October 2022, which allows for sponsors to discuss the RWE study protocol with agency staff before initiation. This program aims to ensure RWE study designs and the proposed data processing approach meets the approval requirement, subsequently promoting coherent regulatory decision making.[49]

Privacy & Security Issues

The limit of access to data is one of the challenges for pharmaceutical companies or researchers when conducting RWE studies.[46] There is always a contradiction between data security and privacy, and the use of RWD. RWD could process a massive amount of personal sensitive data, such as health status, medical histories, financial status, social patterns and correlations.[38] During RWE studies, information from different databases (e.g. eHR, claims etc) may be retrieved and linked for analysis. This poses privacy risks for any unauthorized use or unlawful surveillance of data to reveal personal pattern and correlations.

Currently, many countries worldwide have imposed regulations regarding data protection. For example in UK and EU, the collection, storage, sharing and analysis of healthcare data are governed under the international privacy law, General Data Protection Regulation (GDPR).[50] To balance the need for data protection and facilitate RWE research, appropriate legal basis should be established. Defined guidelines should be available for researchers and pharmaceutical companies to ensure data privacy principles (lawfulness, fairness and transparency, purpose limitation, data minimization, storage limitation, integrity and confidentiality, and accountability) could be achieved throughout the big data security lifecycle (data collection, data transformation, data modelling, and knowledge creation phases).[38] The regulations need to be up-to-date and compatible with the evolving big data technology and its data security technology. Some examples of state-of-art approaches and technologies to control data privacy includes authentication by transport layer security (TLS) or secure sockets layer (SSL); data encryption algorithms; data-masking by k-anonymization and differential privacy; access controls based on roles and attributes; monitoring and auditing of network traffics to prevent intrusion.[51]

THE APPLICATION OF RWD / RWE IN WHOLE PRODUCT LIFECYCLE

RWD has long been used for pharmacovigilance activities and post-marketing effectiveness assessment. Other potential usages of RWD / RWE have been assessed in pre-market authorization stages of the product lifecycle by regulators. RWD is a great data source for studying disease epidemiology, treatment patterns and outcomes, and burden of disease.[52, 53] RWD helps streamline the drug development process, provides evidence for effectiveness for new medical innovations, drives the repurposing of post-market drugs, and may transform healthcare decision making.[52] In addition to supporting pharmacovigilance activities, other usages of RWE throughout the product lifecycle are discussed below.

Early drug development: Application on disease strategy and providing insight for research

The influence of RWD could happen early in drug discovery stages, through identifying unmet needs and burden in disease management. Researchers could assess RWD for studying disease epidemiology information such as incidence and prevalence of a disease, risk factors for disease, and to project opportunities of preclinical developments.[54, 55] RWE plays an important role in research concerning chronic diseases, as RCTs are often time limited.[56] Kong et.al[57] conducted a cross-sectional study based on the data retrieved from Joint Asia Diabetes Evaluation (JADE) register database, to explore the patterns of insulin usage and glycaemic control in Asian people. Through the RWD source, the study was able to identify the association of multiple factors on HbA1c target attainment and hypoglycaemic events, such as type of insulins, diabetic kidney disease status and young-onset diabetes. The study revealed an unmet medical need of a generally poor glycaemic control in Asian population, and called for further support on diabetes research, patient education and engagement.

Application on Clinical study

While designing a traditional RCT, restrictive criteria is imposed in the trial protocol to ensure internal validity of the study. Very often, these criteria lack support and may hamper the generalizability of the study. There were numerous cases of post-marketing withdrawal due to safety issues when the drugs are applied to a broader patient population. These incidences alerted regulators regarding the limitation of RCTs.[53] RWE can assist the modification of RCT design by optimizing patient recruitment criteria. The selection criteria could be based on the evaluation of information such as target patient demographics, disease risk factors, treatment options from RWD. Besides, RWE could also aid in the estimation of required sample size,[58] and aid in the selection of suitable surrogate markers.[55]

RWD can also provide historical controls for clinical trials, and has long been used as a source for historical controls. There are situations where RCTs are not feasible, such as ethical barriers to use inferior treatment options in the control group, or recruitment difficulties in the studies of rare diseases.[59] One early example of using historic controls for approvals by a regulatory agency was Lepirudin in 1998. Lepirudin is used in the treatment of immunologic type of Heparin-associated thrombocytopenia. The source of RWD used was registry data on subjects who was not treated with the recombinant hirudin. When comparing the treatment and historical control group, the study demonstrated a lower incident rate in the treatment group.[60] Although Lepirudin was later discontinued due to commercial decision, the

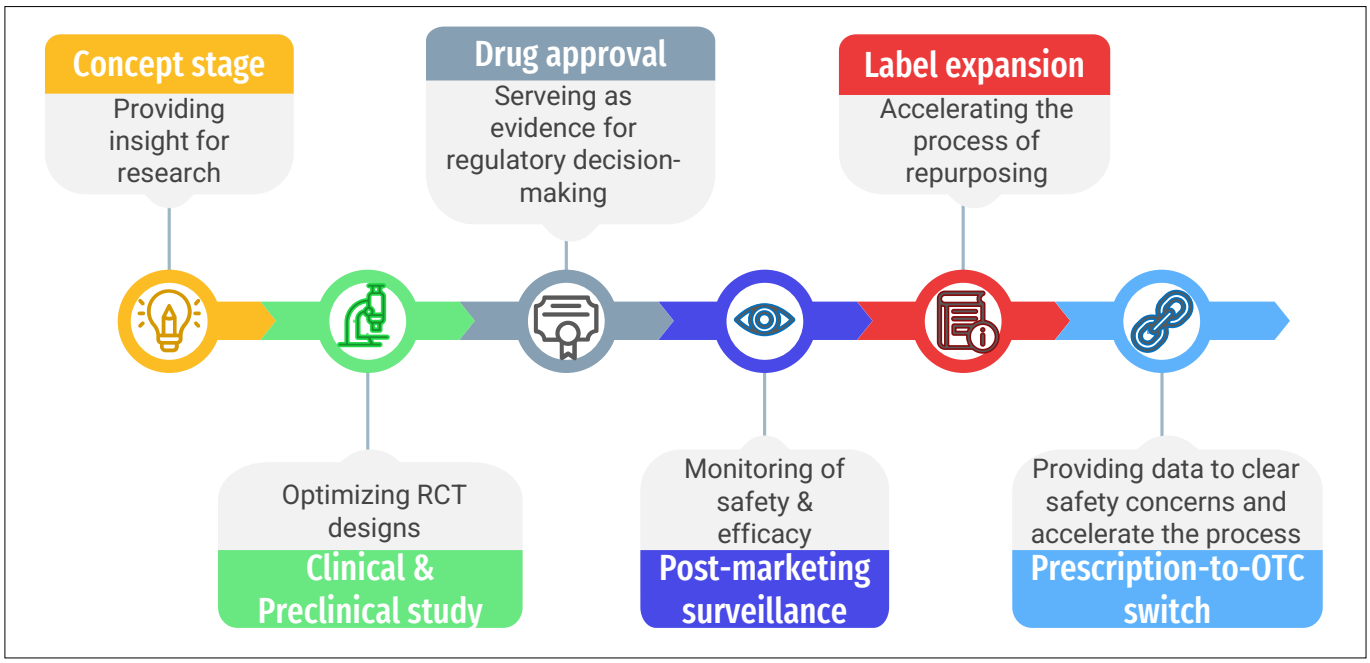

***Figure 3**: Application of RWD/ RWE in pharmaceutical products lifecycle*

case opened the door to RWE as a support for regulatory drug approval. Over the years, the use of RWD for new drug application has extended to different therapeutic areas, with the most common areas being oncology, rare metabolic diseases and immunology.[61]

Supporting post-marketing activities

Aiding post-marketing safety and efficacy studies

The benefit-risk profile surveillance of post-marketing medical products is an acknowledged application of RWD and RWE. According to a systemic review on the types of evidence used in post-marketing authorisation referrals in European Union from 2013-2017,[62] RWE used in non-interventional studies provided evidence for 59% and 34% of 52 referrals for the evaluation of drug safety and drug efficacy respectively. Instead of primarily using it as leading evidence for regulatory decision-making, most of the RWE used in the referrals are cited as substantial evidence when comprehensive assessment was conducted.

One recent example of using RWE in addressing post-marketing safety concern was on the association between ibuprofen and severe coronavirus disease 2019 (COVID-19) infection.[63] Following the first detection of COVID-19 in late 2019, there was a hypothesis that the use of nonsteroidal anti-inflammatory drugs (NSAIDS) could promote the symptoms of COVID-19. A nationwide research conducted in Demark based on the data from Danish National Patient Registry resolved the concern. The study compared the outcomes of COVID-19 between NSAID users and non-NSAID users, in terms of mortality, hospitalisation and intensive care admission. The study confirmed that there is no significant difference between the two groups of patients across different COVID-19 outcomes.[64]

Expanding labelling & indications

The procedures for repurposing existing drug entities for new approvals are not straightforward. Many of the approved new indications still involved RCTs. A proper clinical trial is conventionally recommended to support labelling change to minimize patient risk from off-label usage of drugs. However, RCTs are known to be costly and time-consuming. In U.S., E.U and some other countries, temporary market exclusivity or similar incentive programs are used to encourage manufacturers for conducting trials for drug repurposing. However, these incentive programs many become valueless for market authorization holders if the off-label use of its generic competitors is common in routine prescription.[65]

The adoption of RWE for new indication approvals is a policy advancement of FDA and may accelerate the process.[66] Between 2012 and 2019, 10 products (including one device) submitted their new indication application with the support of RWE to EMA and FDA. Japan is one of the frontier Asian counties in exploring RWE.[61] In 2016, it approved the use of the second-generation selective oestrogen receptor modulators, Raloxifene, in osteoporosis, based on RWE study using retrospective analysis of hospital claims database.[53, 67]

Prescription-to-OTC switch

Prescription-to-over-the counter (Rx-to-OTC) switches is a conceivable opportunity for RWE. Rx-to-OTC switch is the change in marketing status from prescription drug product to non-prescription item. It is recognized by FDA as an important step to improve patient access to effective drug, empower patients on their own healthcare, and lower the healthcare burden due to unnecessary medical care.[63, 68] Rx-to-OTC switch is a data-driven process, which needs to be supported by established scientific evidence on drug safety and efficacy. According to a report from IQVIA, a leading data and analytics solution provider in life science industry, RWE could provide information to access patient's ability to self-diagnosis, self-medication and economic benefits related to switching. These are all critical concerns to address before any switches decisions.[69]

REAL WORLD STUDY IN HONG KONG

In Hong Kong, the number of published studies utilizing RWD increased significantly after the implementation of eHR system in 2016. In 2022, a retrospective cohort study was conducted on the effectiveness of the two antivirals available for COVID-19 patients in Hong Kong, molnupiravir and nirmatrelvir-ritonavir.[70] Using eHR from the Health Authority as a major RWD source, the timeline of the study from commencement to publication was significantly shortened into 8 months; and a significant number of samples was collected from 40,000 hospital in-patients. The study provided timely clinical evidence to support the use of antivirals in the ongoing pandemic of COVID-19.

The use of eHR data in Hong Kong is protected under Cap. 625 Electronic Health Record Sharing System Ordinance and Cap 486 Personal Data (Privacy) Ordinance.[71, 72] Most local real-word studies based on eHR are at institutional level or in public hospitals. Currently, the Hospital Authority is opening access of clinical data to universities for use in research through the Clinical Data Analysis and Reporting System (CDARS). However, the access such data by private pharmaceutical companies are still planning afoot. Hong Kong has outlined the ambition to become a world-leading biotechnology data hub, but there is a need to strengthen Hong Kong's health data infrastructure, and promote academic-industry collaboration and technology transfer.[73] However, as Hong Kong has strong research credentials, many multinational pharmaceutical companies choose Hong Kong as one of the major sites to conduct clinical trials in Asia.[73] As RWD has been exercising its potential in aiding clinical trials worldwide, Hong Kong must catch up with the trend and come up with a balanced solution to

allow greater availability of health data whilst minimising risks to privacy and security.

ROLE OF PHARMACIST IN THE ERA OF REAL-WORLD DATA

Evidence-based pharmaceutical care is an imperative concept that shifted the modern role of pharmacists. In addition to evidence from RCT, it is increasingly important to consult practice-based evidence to support clinical decision making. RWD is a powerful data source to support the generation of these evidence.[74]

Entering the era of real-world data, pharmacists may find growing responsibility in interpreting and evaluating RWE in the decision-making process. Shirley Wang, the principal investigator of the FDA Sentinel Innovation Centre, provided advices for new reviewers on assessing and interpreting RWE studies.[75] To ensure a piece of RWE is applicable, reviewing the relevancy of research question, the validity of the study design and the quality of data is a systematic approach. Identifying the research question is the priority. The PICOT framework is a helpful tool to access whether the RWE is relevant to the clinical inquiry or needs to be addressed, in terms of Population (P), Intervention (I), comparator (C), outcome (O) and Timing (T). While RWE studies are usually complex in study design, reviewer should be acquainted with the basic knowledge of strength and weakness of each type of RWE in different setting. One problem of RWE is that they usually report vague temporality. One simple way is to look for a study design diagram in the paper or construct one by oneself for interpretation of appropriateness of study entry point, and follow-up timing.[76] The relevancy of the data determines the credibility of the research. Data Reliance is the question of whether the data is complete and accurate. While most pharmacists are not well-trained in data science, as a reviewer, we could look for any description in data collection, cleaning, quality control and transformation in the paper and any attempts to address potential information bias.[75]

Besides acting as a reviewer for RWE, pharmacists and other healthcare professionals should be more alert of their subtle participation in the RWE studies. To make eHR and other source of RWD develop into a fit-for-purpose research dataset and facilitate the generation of high-quality clinical evidence, this may also require pharmacists to provide domain expertise from time to time. When conducting RWE studies, communication between data scientist and healthcare professionals is valuable to balance the need of technical feasibility and addressment to clinical realities. Furthermore, as research data are generated from routine clinical practice in RWE studies,[74] quality assurance and control processes should start from data entry. As data could be expanded from one single patient to a potential cohort of patients who might benefit from RWE studies, pharmacists must remain vigilant in securing informatics competencies.

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Overview of the Drug Therapy of Psoriasis

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease that is characterised by the appearance of well-delineated red and silvery scaly plaques that varies in extent from a few patches to generalised involvement. Research has shown that psoriasis is caused by both genetic and environmental factors. It is a chronic relapsing disease which requires long term therapy. The choice of therapy for psoriasis depends on the disease severity, relevant comorbidities, patient's preferences and evaluation of patient's response. Mild to moderate psoriasis can be managed by topical agents including corticosteroids and vitamin D analogues, while moderate to severe psoriasis will require phototherapy or systemic treatment. This article provides an overview of the background and treatment therapies of psoriasis, from the conventional topical and oral medications to the promising new therapy of biologics.

Keywords: *Psoriasis, Inflammation, Skin, Phototherapy, Topical, Biologics*

INTRODUCTION

Psoriasis is a complex immune-mediated inflammatory disease affecting about 2% of the population worldwide.[1] It occurs in genetically susceptible individuals and presents with the development of inflammatory plaques on the skin. Although genetics plays a role in the disease, patients may not have positive family history. Other factors that may trigger psoriasis include: smoking, alcohol, obesity, skin injury and some common medications. The disease can have a significant effect on the quality of life of patients.

Patients with psoriasis are at increased risks of comorbidities, including, but not limited to, psoriatic arthritis, cardiovascular disease, diabetes mellitus, obesity, inflammatory bowel disease and non-alcoholic fatty liver disease compared with the general population. The epidemiological studies of psoriasis allow us to understand the pathogenesis contribution, so as to reveal predisposing genetic and autoimmune traits in the process of the disease. The ideal goal of treatment with psoriasis is to optimise the controls of symptoms, improve quality of life, prevent psychological comorbidity, as well as structural damage and disability. This review will give an overview of the background of psoriasis and its management.

PATHOPHYSIOLOGY

Recent studies have provided better insight into the immune system's role in the pathogenesis of psoriasis. Inciting events that propagate psoriasis begin with the stimulation of plasmacytoid dendritic cells through complexes consisting of host DNA with keratinocyte produced cathelicidins, leading to the subsequent release of interleukin (IL)-12 and IL-23.[2] The signalling pathway for the production of IL-23 is mediated intracellularly by the Janus Kinase (JAK) pathway. Production of these cytokines stimulates differentiation of naïve T cells to T-helper (Th) 1 and Th17 cells. This ultimately leads to the production of tumour necrosis factor (TNF)-alpha, IL-22, and IL-17, causing hyperproliferation of keratinocytes and vascular endothelial growth factor-induced angiogenesis.[3] **(Figure 1)**[3] Stimulation of keratinocytes leads to additional release of immune-mediating complexes and chemoattractants, resulting in a self-perpetuating cycle.[4] The inflammatory cascade in patients with psoriasis is not contained solely to the skin. Systemic inflammation is associated with a high risk of comorbid illnesses. Hence, novel therapies for psoriasis are directed at interrupting this immune-mediated cycle.

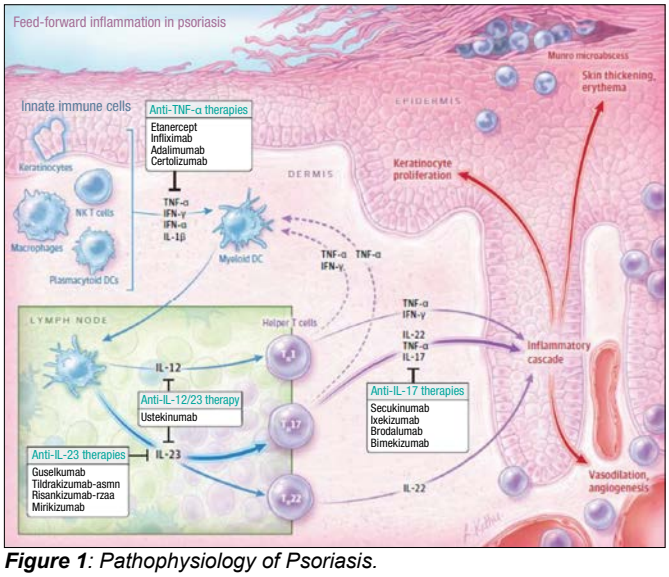

Figure 1*: Pathophysiology of Psoriasis.*

CLINICAL MANIFESTATIONS

Psoriasis occurs in a variety of clinical forms and may exhibit different features depending on the body area that it affects. The most common subtype of psoriasis is plaque psoriasis, representing 90% of all manifestations of psoriasis.[5] The three other less frequently observed subtypes are guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. Although one subtype typically predominates in one patient, different subtypes may also coexists in an individual patient at one time.

Classical clinical manifestations in plaque psoriasis are sharply demarcated raised lesions covered in silvery scales. The elbows, knees and scalp are the most common sites for involvement, and the extent of involvement can range from localised area to involvement of the majority of the body surface area. The plaques may be asymptomatic, but pruritus is common. Painful fissures can also occur in the involvement of the palm or sole of patients.

Guttate psoriasis is a particular form of psoriasis with the appearance of multiple small, psoriatic salmon-pink papules and plaques, which are usually 1-10 mm in diameter and predominantly appears on the trunk. A strong association between group A streptococcal infection and guttate psoriasis has been identified. Also, about one third of guttate psoriasis would progress to chronic plaque psoriasis.[6]

Erythrodermic psoriasis is an uncommon form of psoriasis that is treated as a dermatological emergency as it can be associated with electrolyte imbalance and sepsis.[7, 8] It is characterised by the development of erythema, scales and exfoliation of the skin involving over 75% of the body surface area. The affected skin is often painful and itchy. Systemic symptoms such as fever, chills, tachycardia and malaise may also occur in patients with erythrodermic psoriasis.[9]

Another rare subtype of psoriasis is pustular psoriasis with life-threatening complications including skeletal and joint disease, as well as renal and hepatic abnormalities. It presents with the acute onset of widespread painful erythema, scaling and areas of superficial pustules.[10, 11]

CHOICE OF THERAPY

Selecting an appropriate treatment modality for psoriasis should be matched to the severity of the disease while considering the presence of any comorbidities. For most patients with mild plaque psoriasis, topical therapies are recommended initially, which are usually sufficient to achieve the recommended goals. For patients with moderate to severe disease, systemic therapies alone or in combination with topical agents are typically required. **(Figure 2)**[3] shows an algorithm for the general approach to treatment that incorporates both classification systems - mild vs. moderate to severe, and topical vs. systemic therapy. Moderate to severe psoriasis is typically referred to as involving more than 5 to 10 percent of the body surface area or the involvement of face, palm or sole, or disease that is otherwise disabling. As the application of topical therapy to a large body surface area is not practical, those patients with more than 5 percent of body surface area affected are generally candidates for phototherapy or systemic therapy. At all times, the risk and benefit of treatments should be discussed with patients, and a shared decision-making process should be applied to the selection of an appropriate therapy that will achieve the target goals and meet the patient's expectation. Although medication safety plays an important role in treatment selection, this must be balanced by the risks of undertreatment of psoriasis, leading to inadequate clinical improvement and patient dissatisfaction.

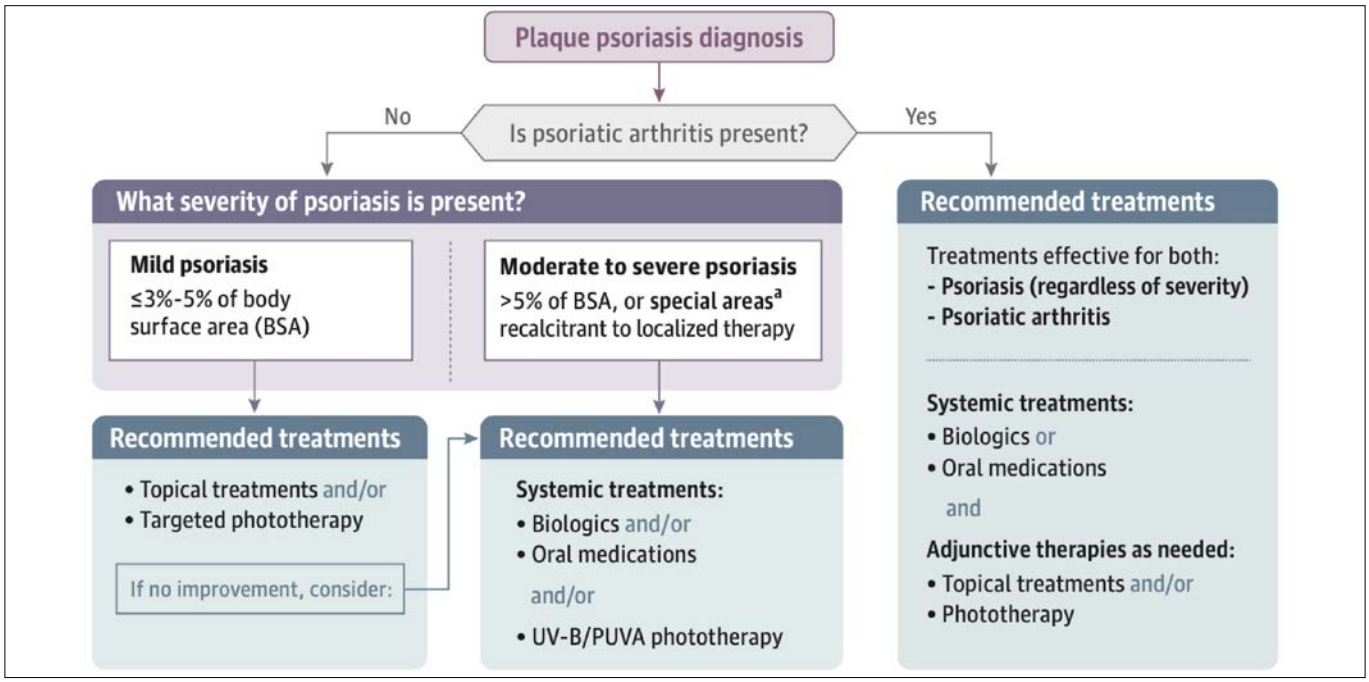

***Figure 2**: Overall Treatment Approach for Plaque Psoriasis.*

TOPICAL THERAPIES

Topical medications are the most common agents used to treat patients with mild to moderate psoriasis. They are also frequently used as adjunctive therapies for patients on phototherapy, systemic or biologic therapy. Patient adherence is the largest factor to successful treatment with topical therapies.[12] One of the most valuable and inexpensive topical adjunct is emollient. Maintaining psoriatic skin soft and moisturised is important as it can help with itching and irritation. Other agents include topical corticosteroids, topical vitamin D analogues (calcitriol and calcipotriol), topical keratolytics (tazarotene, salicylic acid, urea), topical calcineurin inhibitors (pimecrolimus and tacrolimus), and tar.

Topical Corticosteroids

Topical corticosteroids are the cornerstone of psoriasis despite the developments of newer therapies. They are often effective and well tolerated, especially in patients with mild psoriasis. They help with inflammation and proliferation of psoriatic skins, as well as exert their locally vasoconstrictive effect through a down regulation of genes coding proinflammatory cytokines.[13] Hence, making it a useful therapy for this immune-mediated disease. To minimise the adverse effects and maximise adherence, the choice of topical corticosteroids is very important. Topical corticosteroids are available in a wide range of preparations including cream, gel, ointment, foam, lotion, and spray. Studies show that the vehicle can directly affect a preparation's therapeutic and adverse effects by changing the pharmacokinetics of the topical corticoid molecule.[14, 15] In addition, different potency of corticosteroids will have different efficacy and may be chosen for different parts of the body to treat psoriatic skin. Lower potency corticosteroids are particularly recommended to apply on the face, groin, axillary areas, and in infants and children, while mild and high potency corticosteroids are mainly used for initial therapy and all other parts of the body. Super potent corticosteroids are reserved for stubborn, cutaneous plaques or lesions on the palms, soles, and scalp.[16] In clinical practice, to achieve a faster improvement of lesions, a high potency or super potent corticosteroids are often chosen as an initial therapy. However, they should not be used for more than 2 weeks and if longer treatment durations are required, the patient should be under close clinical supervision.[17-18]

Although the adverse effects of corticosteroids tend to be more severe with systemic rather than topical treatment, risk of systemic side effects associated with chronic topical corticosteroid use increases with high potency formulations. With frequent and prolonged use of high potency topical corticosteroids on skin or intertriginous areas, the adverse effects may include skin atrophy, telangiectasia, and striae. Regular examinations by physicians are recommended. Other systemic adverse effects such as suppression of the hypothalamus pituitary and adrenal gland axis is rare and can be minimised by limiting long-term use of high potency topical corticosteroids on large body surface areas, especially limiting such use in children.[19, 20] Special attention should also be paid when applying topical corticosteroids in the presence of an infection, as there is a risk of exacerbation. Topical corticosteroids can inhibit the skin's ability to fight against bacterial or fungal infections.[21] Hence, balancing between the adverse reactions of corticosteroids and maintaining its efficacy at the same time has been a great challenge to researchers and physicians.

Topical Vitamin D analogues

Topical vitamin D analogues for the treatment of psoriasis includes calcitriol and calcipotriol. The mechanism of action of topical vitamin D analogues involves the drug's ability to inhibit keratinocyte proliferation and boost keratinocyte differentiation.[22] In addition, vitamin D analogues bind to vitamin D receptors on T cells and inhibit T cell proliferation and other inflammatory mediators.[23] The efficacy of topical vitamin D analogues are modest when used alone and in the same preparation, calcitriol and calcipotriol are equally effective.[24, 25] However, on the sensitive and intertriginous areas of the skin, calcitriol appears to be less irritating than calcipotriol. Perilesional erythema, perilesional oedema, and stinging or burning sensations were less common in the areas treated with calcitriol than calcipotriol. In another systemic review of randomised controlled trials, calcipotriol exerts the same effectiveness as potent topical corticosteroids and calcitriol.[26] Combined use of calcipotriol and potent corticosteroids also increases clinical response and tolerability in clinical trials compared with either agent used alone.[27, 28] Hence, topical calcipotriol may serve as an alternative or adjunct to topical corticosteroid therapy. The most common adverse effects of topical vitamin D analogues include skin irritation, burning sensation, pruritus, and oedema. Systemic absorption generally does not result in adverse outcomes unless patient has severe renal failure.[29, 30]

Topical keratolytics

Topical keratolytic agents include topical tazarotene, salicylic acid and urea. Topical tazarotene is a retinoid that inhibits proliferation of keratinocytes and helps to break down the thick scales on the plaque. In two randomised controlled trials, it was shown that it was safe and effective, with up to one-third of patients experienced at least 50% improvement of psoriasis after 12 weeks.[31] Adverse effects may include irritation and burning sensation on the skin. Salicylic acid is the most commonly used keratolytic compound. It exerts an increasingly potent, rapid, and deep keratolytic effect on the stratum corneum which leads to descaling in psoriatic skins.[32] Topical urea is useful in treating plaque psoriasis upon its keratolytic, hydrating, hygroscopic, penetration-enhancing, epidermis-thinning, and anti-pruritic effects. The moisturizing action of urea in dry and scaly psoriatic skin has been widely studied and is well accepted.[33, 34] They are usually well tolerated with only non-systemic side effects reported, with mild irritation being the most common.

Topical calcineurin inhibitors

Topical tacrolimus 0.3% and 0.1%, and pimecrolimus 1% are effective in the treatment of psoriasis in sensitive areas such as the face, axillary, and groin regions. They work by blocking T cell activation through inhibiting the synthesis of IL-2 and interferon gamma (IFN-γ), hence exerting its immunomodulatory effect.[35] In a randomised, double-blind, vehicle-controlled study, up to 71% of patients experienced clear or almost clear psoriasis after eight weeks treatment with topical pimecrolimus 1% compared with placebo.[36] Tacrolimus 0.1% ointment has also shown its effect in clearing psoriatic lesions in another eight-week, randomised, double-blind, vehicle controlled trial with 167 patients ages 16 and older, using twice-daily treatment on intertriginous and facial lesions with tacrolimus 0.1% ointment. 65% of patients achieved excellent improvements compared with placebo in the study.[37] Common adverse effects with topical use of calcineurin inhibitors include skin irritation, especially in highly inflamed lesions. This can be reduced by treating first with topical corticosteroids before transitioning to topical calcineurin inhibitors.

Tar

Topical tar preparations include shampoo, cream, lotion, ointment and oil. Its exact mechanism of actions are not yet fully discovered but it may involve aryl hydrocarbon receptors to exert its anti-inflammatory and anti-proliferative effect.[38, 39] Choosing tar as treatment option has become less popular with newer and less messy alternatives, but it still serves as a useful adjunct to topical corticosteroids therapy.

PHOTOTHERAPY

Phototherapy consists of exposure to specific wavelength of light. It has been used for years to treat patients with plaque psoriasis and has long been recognised as beneficial for the control of psoriatic skin lesions. Unlike sunlight, phototherapy delivers specific wavelengths that are therapeutic for psoriasis, and it minimizes emission of wavelength responsible for carcinogenesis.

A targeted phototherapy such as excimer laser can be used to treat localised mild plaque psoriasis. It emits high intensity ultraviolet B (UVB) of 308 nm and a considerably higher dose can be administered to psoriatic plaques at each treatment session when compared to traditional phototherapy.[40] It is also particularly useful for treating psoriasis plaques that are located in difficult areas such as scalp, palms, knees, elbows and soles. In some uncontrolled trials, it is suggested that laser therapy has more efficient responses than conventional phototherapy. Patients achieved the outcome of better percentage of clearing of plaques than those typically required phototherapy.[41, 42] Excimer laser therapy has very low carcinogenic potential and the main adverse effects are a burning sensation and blistering.

A full-body-surround phototherapy is used to treat more extensive psoriasis. However, since the emerging of new biologics treatment, the use of phototherapy for moderate to severe psoriasis has drastically decreased. The main types of phototherapy for moderate to severe psoriasis includes narrowband UVB, broadband UVB, and psoralen plus ultraviolet A (PUVA). Narrowband UVB involves in delivering 311 nm of radiation while broadband UVB aims to deliver 290 to 320 nm of radiation. PUVA involves treatment with a photosensitiser (either oral or bath psoralen) followed by ultraviolet A (UVA) radiation of 320 to 400 nm. The theory behind UVB phototherapy is that it decreases DNA synthesis, leading to keratinocyte apoptosis and decreased production of proinflammatory cytokines by T cells.[43, 44] Compared with broadband UVB, narrowband UVB are more commonly used due to greater efficacy, longer duration of remission, lower photocarcinogenic potential and less erythema upon the use of same physical dose.[45] As for PUVA, psoralens are used to intercalate into DNA to supress DNA synthesis.[46] Hence, exerting its therapeutic effect through its immunomodulatory properties. Although treatment with PUVA is more efficient than UVB, it is no longer preferred due to the development of skin cancer with long term use. Long term studies have shown a dose-related increase in the incidence of nonmelanoma skin cancers among patients exposed to high cumulative doses of oral PUVA.[47-49] Patients who have received prolonged courses of PUVA are required to have ongoing monitoring. Adverse events of PUVA include gastrointestinal upset, burning, pruritus, hypertrichosis, and photoaging. In general, phototherapy is contraindicated in patients with a history of melanoma or extensive non-melanoma skin cancer.

SYSTEMIC THERAPY

Small molecules

Traditional systemic treatment options for psoriasis include methotrexate, cyclosporin A and retinoids. All of them are oral drugs with the exception of methotrexate, which is also available for subcutaneous administration.

Methotrexate

Methotrexate is a folate antagonist that inhibits dihydrofolate reductase, thereby inhibiting DNA synthesis by blocking thymidine and purine biosynthesis. The mechanism of action involved in psoriasis includes the antiproliferative effects of methotrexate on DNA synthesis in epidermal cells, and also its immunosuppressive effects on activated T cells that control psoriasis.[50] When compared to biologics, methotrexate seems to be less effective than some of them. In a randomised controlled comparative study of methotrexate, adalimumab and placebo, 271 patients with moderate to severe plaque

psoriasis were randomized to receive oral methotrexate 7.5 mg to 25 mg per week, adalimumab 40 mg every other week, or placebo. After 16 weeks, the proportion of patients achieving over 75% improvement in Psoriasis Area and Severity Index (PASI 75) with methotrexate was more than placebo but less than adalimumab.[51] Similar results were shown in another study using subcutaneous methotrexate in patients with moderate to severe plaque psoriasis.[52] The most common side effects of methotrexate include nausea, leukopenia and liver transaminase elevation, as well as increased risk of hepatic, pulmonary, hematologic and renal toxicity. Folic acid may protect patients against some of the common side effects seen with low dose methotrexate. Despite the potential side effects and its hepatotoxicity, it remains a frequently used cost-effective first-line drug. Close monitoring of liver and renal function, and regular full blood counts allows the long term administration of methotrexate feasible.

Cyclosporin

Cyclosporin is a T cell inhibiting immunosuppressant and is effective in patients with severe psoriasis. It belongs to the group of calcineurin inhibitors and exerts it anti-psoriatic effects by reducing production of IL-2. The use of cyclosporine in psoriasis was based on studies supporting its status as a highly and rapidly effective treatment in achieving up to 80% clear of psoriasis.[53] In addition, a meta-analysis of 3 major studies on the use of cyclosporin in 597 patients with severe plaque psoriasis revealed that cyclosporin given at a dosage of 2.5 and 5 mg/kg/day was significantly superior to etretinate, a synthetic retinoid indicated to treat severe psoriasis. In addition, cyclosporine 1.25 mg/kg/day was proved to be significantly more effective than placebo.[54] Hypertension, renal toxicity and non-melanoma skin cancer are significant potential side effects. Hence, close monitoring is required and often limit the long term use of cyclosporin in patients with psoriasis.[55]

Acitretin

Acitretin is a retinoid, belonging to derivatives of vitamin A, used in the treatment of moderate to severe psoriasis, including pustular and erythrodermic forms. The mechanism of action of acitretin in psoriasis involves normalising of keratinocyte proliferation and differentiation, as well as affecting the transcriptional processes by acting through nuclear receptors.[56, 57] The efficacy of acitretin was shown in a multi-centred, randomised study which reported 22.2% and 44.4% of patients reaching PASI 75 and PASI 50 at 24 weeks.[58] Dry lips, hair loss, skin peeling, pruritus and nail disorders were the most frequently reported side effects of acitretin. Monitoring for hypertriglyceridemia and hepatotoxicity are also required with acitretin treatment. It is worth noting that acitretin is teratogenic and it is only indicated in men and in women of non-reproductive potential. Pregnancy is contraindicated for three years after discontinuing the drug.[59]

Biologic agents

Development of biologic therapies that specifically target immune mediators involved in the pathogenesis of psoriasis has significantly improved the likelihood that patients can achieve clear or almost clear skin. Emerging evidence also suggests that the ability of these agents to supress the underlying systemic inflammation has long-term benefits on the various comorbidities associated with psoriasis. Currently, 11 biologic agents are marketed in the United States with evidence in managing plaque psoriasis.

1. Tumour necrosis factor-alpha (TNF-α) inhibitors: Adalimumab, Certolizumab, Etanercept, Infliximab
2. IL-12/IL-23 inhibitors: Ustekinumab
3. IL-17 inhibitors: Brodalumab, Ixekizumab, Secukinumab
4. IL-23 inhibitors: Guselkumab, Risankizumab, Tildrakizumab

All biologics used to treat psoriasis are administered subcutaneously except infliximab, which is administered intravenously. Overall, side effects that occur at slightly higher rates than placebo are common to all biologics including injection site reactions, nasopharyngitis, and upper respiratory tract infections.

TNF-α inhibitors

TNF-α inhibitors are the oldest class of currently approved biologics for the treatment of psoriasis. By inhibiting TNF-α, these biologics decrease the downstream inflammatory cascade taking part in the psoriasis pathogenesis.

Etanercept was the first TNF-α inhibitor approved by the United States Food and Drug Administration (FDA) for psoriasis. It is different from others in the biologic category in that it is not a monoclonal antibody, but rather a recombinant human fusion protein between a TNF-α receptor protein and the crystallisable fragment portion of IgG1. It competitively inhibits the interaction of TNF with cell surface receptors, preventing TNF-mediated cellular responses and modulating the activity of other proinflammatory cytokines that are regulated by TNF in psoriasis.[60] Etanercept's safety and efficacy was illustrated in a global phase III randomised controlled trial. It was shown that etanercept provided clinically meaningful benefit to patients with chronic plaque psoriasis when compared to placebo group, with no apparent decrease in efficacy after dose reduction.[61] Standard adult dosing for etanercept is subcutaneous injection of 50 mg twice weekly for the initial three months of therapy, followed by a 50 mg injection once weekly for maintenance therapy.

Infliximab was first approved for the treatment of plaque psoriasis by the FDA in 2006. It is a chimeric IgG1 monoclonal antibody that binds to soluble and transmembrane forms of TNF-α, thereby interfering with

endogenous TNF-α activity.[62] Its safety and efficacy was established in a phase III, multicentre, double-blind trial. In this trial, 378 patients with moderate to severe plaque psoriasis were allocated in a 4:1 ratio to receive infusions of either infliximab 5 mg/kg or placebo at weeks 0, 2, and 6, then every 8 weeks to week 46. It was shown that infliximab is effective in both an induction and maintenance regimen for the treatment of moderate to severe psoriasis, with a high percentage of patients achieving sustained PASI 75 and PASI 90 improvement through 1 year.[63] Standard dosing for infliximab for adults is intravenous infusion of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks thereafter.

Adalimumab, a human monoclonal antibody against TNF-α was originally used for patients with rheumatoid arthritis, and then later on approved by the FDA for treatment of adult patients with moderate to severe chronic plaque psoriasis in 2008. The mechanism of action is based on both the neutralisation of TNF-α bioactivity and the induction of apoptosis of TNF-expressing mononuclear cells.[64] Adalimumab has illustrated its efficacy and safety in several clinical studies. A controlled phase III trial of 1212 patients randomised to receive adalimumab 40 mg or placebo every other week for the first 15 weeks shown that 71% of adalimumab and 7% of placebo-treated patients achieved PASI 75 at week 16. In addition, continuing adalimumab resulted in a higher percentage of patients maintaining their response at week 52.[65] Standard dosing for adalimumab for adults is an initial subcutaneous injection of 80 mg, followed by 40 mg given every other week, beginning one week after the initial dose.

Certolizumab is a pegylated humanized antibody fragment with specificity for TNF-α. It binds to human TNF-α and neutralises the pathological inflammation caused by the cytokine. In 2018, the FDA approved the drug for the treatment of adults with moderate to severe psoriasis. Support for the use of certolizumab comes from two phase III randomised trials CIMPASI-1 and CIMPASI-2. Patients with moderate to severe chronic plaque psoriasis were randomised in a ratio of 2:2:1 to certolizumab 400 mg, certolizumab 200 mg, or placebo every 2 weeks. At week 16, certolizumab-treated patients achieving a PASI 50 continued treatment through week 48. It was concluded that treatment with either certolizumab 400 mg or 200 mg every 2 weeks was associated with significant and clinically meaningful improvements in moderate to severe psoriasis. The 400 mg dose could provide additional clinical benefit and safety profile was consistent with the therapeutic class.[66] A point worth noting is that unlike other anti-TNF-α agents, certolizumab has no fragment crystallizable region, and is thus not actively transported across the placenta. Hence, it is approved for use during pregnancy and breastfeeding.[67] Standard dosing for certolizumab is 400 mg every other week. An optional regimen for patients who weigh ≤90 kg is 400 mg at weeks 0, 2, and 4, followed by 200 mg every other week.

IL-12/IL-23 inhibitors

Ustekinumab is a human monoclonal antibody that targets both IL-12 and IL-23, with it being the only biologic that inhibits both IL-12 and IL-23 through inhibition of their shared p40 subunit. The FDA approved its use to treat psoriasis in 2009, and is now indicated for the treatment of adults and children 12 years and older with moderate to severe psoriasis. The therapeutic effect of ustekinumab is primarily mediated through its inhibition of IL-23. Two phase III trials, PHOENIX-1 and PHOENIX-2, has demonstrated the efficacy and safety for ustekinumab. In PHOENIX-1, 766 patients with moderate to severe psoriasis were randomly assigned to receive ustekinumab 45 mg (n=255) or 90 mg (n=256) at weeks 0 and 4 and then every 12 weeks, or placebo (n=255) at weeks 0 and 4, with subsequent crossover to ustekinumab at week 12. 67% patients receiving ustekinumab 45 mg, 66% receiving ustekinumab 90 mg, compared to 3% receiving placebo achieved PASI 75 at week 12. Responders who were kept on therapy generally maintained improvements in psoriasis out to at least week 76. PHEONIX-2 showed similar results, indicating that ustekinumab is an effective treatment for moderate to severe psoriasis, and dosing every 12 weeks maintains efficacy for at least a year in most patients.[68, 69] Dosing of ustekinumab is weight based. Standard dosing for ustekinumab for adults ≤100 kg is 45 mg given at weeks 0, 4, and every 12 weeks thereafter. A 90 mg dose given in the same regimen is recommended for adults who weigh more than 100 kg.

IL-17 inhibitors

To date, there are three human monoclonal antibodies targeting IL-17 available for the treatment of psoriasis. Secukinumab and ixekizumab block IL-17A, whereas brodalumab is directed against the IL-17 receptor A. IL-17A is a naturally occurring cytokine that functions in innate and adaptive immune responses, and specifically mediates effects in antibacterial and fungal immunity and tissue repair.[70] IL-17A acts by activating several cell types, including keratinocytes, fibroblast-like, endothelial cells, chondrocytes, and osteoblasts, and resulting in a release of pro-inflammatory cytokines. Thus, apart from promoting inflammation, hyperproliferation, matrix destruction, vessel activation, bone erosion, and cartilage damage could result.[71] It was found that the level of IL-17A is elevated in psoriatic plaques.

Secukinumab was the first IL-17 inhibitor approved by the FDA for plaque psoriasis in 2015. It selectively binds to IL-17A and inhibits its interaction with several cell types as mentioned above. As a result, it inhibits the downstream inflammatory pathways that drive psoriasis pathogenesis.[72] Two phase III, multi-centred, doubled-blind trials, ERASURE and FIXTURE, had investigated the efficacy and safety of secukinumab in moderate to severe plaque psoriasis versus placebo. In both studies, secukinumab was shown to be superior to placebo in terms of clinical efficacy. In both trials, secukinumab was given as a 300 mg or 150 mg dose once weekly for five weeks, then once every four weeks. In the ERASURE

trial, at week 12, 82% and 72% of patients in the 300 mg and 150mg secukinumab group respectively, achieved a PASI 75, while only 5% of patients in the placebo group achieved the same results. Similar results were found in the FIXTURE trials, where superior efficacy of secukinumab over placebo were demonstrated for PASI 75.[73] Standard dosing for plaque psoriasis is 300 mg given subcutaneously once weekly at weeks 0, 1, 2, 3, and 4 followed by 300 mg every four weeks. Doses of 150 mg are also sufficient for some patients.

Ixekizumab, as a humanised IgG4 monoclonal antibody, selectively binds to IL-17A and prevents IL-17A from binding to the IL-17A receptor. Thus, this attenuates an inflammatory response mediated by IL-17A and disrupts the pathogenic inflammatory cascade of psoriasis.[74] It was approved by the FDA for the treatment for plaque psoriasis in 2016. Ixekizumab's safety and efficacy in plaque psoriasis in adults were established in three phase III clinical trials, UNCOVER-1, UNCOVER-2 and UNCOVER-3, with a total of 3,866 participants with moderate to severe plaque psoriasis. 1296 patients were randomly assigned in the UNCOVER-1 trial, 1224 patients in the UNCOVER-2 trial, and 1346 patients in the UNCOVER-3 trial to receive subcutaneous injections of placebo, 80 mg of ixekizumab every 2 weeks after a starting dose of 160 mg (2-week dosing group), or 80 mg of ixekizumab every 4 weeks after a starting dose of 160 mg (4-week dosing group). At week 12 in the UNCOVER-3 trial, the patients entered a long-term extension period during which they received 80 mg of ixekizumab every 4 weeks through week 60. At week 12 in the UNCOVER-1 and UNCOVER-2 trials, the patients who had a response to ixekizumab were randomly reassigned to receive placebo, 80 mg of ixekizumab every 4 weeks, or 80 mg of ixekizumab every 12 weeks through week 60. In all three trails, ixekizumab was effective and achieved greater clinical response than placebo. Treatment with ixekizumab in the long term has also demonstrated a sustained efficacy in patients with plaque psoriasis.[75] Standard dosing for ixekizumab is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12. Subsequently, 80 mg are given every four weeks.

Brodalumab is an anti-IL-17A monoclonal antibody which has high efficacy for psoriasis. In February 2017, the FDA approved brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients. Efficacy and safety of brodalumab has been supported by the data from phase III randomised trials (AMAGINE-2 and AMAGINE-3). 3721 patients were assigned in a 2:2:1:1 ratio to receive brodalumab 210 mg every two weeks, brodalumab 140 mg every two weeks, standard dosing of ustekinumab on day 1, week 4, and then every 12 weeks, or placebo. At week 12, more patients receiving 210 mg of brodalumab (86%) or 140 mg of brodalumab (67%) achieved PASI 75 compared with 8% of patients in the placebo group in AMAGINE-2, and 85%, 69%, and 6% of patients respectively in AMAGINE-3. In addition, the rate of complete clearance of skin disease (PASI 100) at week 12 was higher among patients given 210 mg of brodalumab compared with patients receiving ustekinumab. 44% vs. 22%, respectively in AMAGINE-2, and 37% vs. 19%, respectively in AMAGINE-3. The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 and 27% in AMAGINE-3. It was concluded that brodalumab treatment resulted in significant clinical improvements in patients with moderate-to-severe psoriasis.[76, 77] Recommended dosing of brodalumab is 210 mg given at weeks 0, 1, and 2 and then every two weeks.

IL-23 inhibitors

In recent years, inhibitors of IL-23 have emerged as safe and effective options for the treatment of moderate to severe plaque psoriasis. Selective IL-23 inhibitors also require less frequent dosing than IL-17 inhibitors. To date, guselkumab, tildrakizumab, and risankizumab have been approved in the last 4 years with targeting of the p19 subunit of IL-23.

Guselkumab is a fully human, IgG1 monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits its signalling. It was approved by the FDA for the treatment of moderate to severe plaque psoriasis in 2017. VOYAGE-1 and VOYAGE-2 were the first phase III trials to evaluated the efficacy and safety of guselkumab in psoriasis treatment. In VOYAGE-1, 837 patients were randomised at a 2:1:2 ratio to receive guselkumab 100 mg at weeks 0, 4, then every 8 weeks, placebo given at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20 then every 8 weeks, or adalimumab 80 mg at week 0, 40 mg at week 1, then 40 mg every 2 weeks. In VOYAGE-2, 992 patients with moderate to severe plaque psoriasis in a 2:1:1 ratio was randomised to receive guselkumab, placebo followed by guselkumab or adalimumab groups, with dosing regimens similar to those in VOYAGE-1. The primary endpoint was compared to placebo and evaluated by an Investigator Global Assessment (IGA) score 0 or 1 (on a scale of 0 to 5, with higher scores indicating more severe disease) at week 16 achieved by 84-85%. PASI 90 was coprimary endpoints and achieved by 70-73%. Guselkumab was also superior to adalimumab at these endpoints. It was concluded that guselkumab shows durable efficacy and a consistent safety profile in patients with moderate to severe psoriasis treated for up to 3 years.[78, 79] Upper respiratory tract infections, tinea and herpes simplex virus infections, arthralgia, diarrhoea, and gastroenteritis are the most common adverse effects of guselkumab. Recommended dosing for guselkumab is 100 mg at weeks 0, 4, and then every 8 weeks.

Tildrakizumab was approved by the FDA for the treatment of moderate to severe plaque psoriasis in 2018. Phase III trials reSURFACE-1 and reSURFACE-2 supports the superiority of tildrakizumab compared with placebo and etanercept. In reSURFACE-1, 772 adults with moderate to severe plaque psoriasis were randomly assigned to receive tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo at weeks 0 and 4 and then every 12 weeks. After 12 weeks, 62%, 64% and 6% of patients in the 200 mg, 100 mg, and placebo groups,

respectively, achieved PASI 75. The reSURFACE-2 trial randomly assigned 1090 patients to similar groups plus an etanercept group. After 12 weeks, 66%, 61%, 6% and 48% of patients in the tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, and etanercept groups, respectively, achieved PASI 75. It was concluded that tildrakizumab 200 mg and 100 mg were efficacious compared with placebo and etanercept and were well tolerated in the treatment of patients with moderate to severe chronic plaque psoriasis.[80] Tildrakizumab had a similar safety profile to guselkumab with nasopharyngitis, headache, and injection-site reaction being the most common adverse effects. Recommended dosing of tildrakizumab is 100 mg given subcutaneously at weeks 0 and 4 and then every 12 weeks.

Risankizumab was approved in the following year 2019 by the FDA as the third IL-23 inhibitor for the treatment of moderate to severe plaque psoriasis in adults. Risankizumab has shown greater efficacy than placebo and ustekinumab in two phase III trials UltIMMa-1 and UltIMMa-2. In the 16-week blinded phase of the 52-week trails, 506 patients in UltIMMA-1 and 491 patients in UltIMMa-2 with moderate to severe plaque psoriasis were randomly assigned to receive risankizumab 150 mg, ustekinumab 45 or 90 mg based upon weight, or placebo in a 3:1:1 ratio. In UltIMMa-1, 75% 42% and 5% of patients, respectively, achieved PASI 90 at 16 weeks. In UltIMMa-2, 75% 48% and 2% achieved this endpoint, respectively.[81] It was concluded that risankizumab was superior to both placebo and ustekinumab in the treatment of moderate to severe plaque psoriasis. Treatment emergent adverse event profiles were similar across treatment groups and there were no unexpected safety findings. The most common adverse events seen in those treating with risankizumab were nasopharyngitis, headache, gastroenteritis and back pain. Recommended dosing for risankizumab is 150 mg at week 0 and week 4, then every 12 weeks.

CONCLUSION

Psoriasis is an inflammatory skin disease that is associated with multiple comorbidities and substantially diminishes patients' quality of life. Although psoriasis cannot currently be cured, management should aim to minimise physical and psychological harm by treating patients early in the disease process, as well as identifying and preventing associated comorbidity, instilling lifestyle modifications, and employing a personalised approach to treatment. With the wealth of research and the developments of newer treatment options, both allows the potential to give patients with psoriasis an improved quality of life and control of key aspects of psoriasis.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Overview of the drug therapy for Psoriasis

1. ***What plays a major role in Psoriasis?***
   A. The nervous system
   B. The digestive system
   C. The circulatory system
   D. The immune system

2. ***The most prevalent form of psoriasis is plaque psoriasis, and it is characterized by –***
   A. Pimples all over the face
   B. White blisters of pus localized on the hands and feet
   C. Sharply demarcated raised lesions covered in silvery scales on their elbows, knees, scalp or the back
   D. White to yellowish flaky scales on the scalp or back of the ear

3. ***Which of the following about Psoriasis is/are true?***
   i. Psoriasis cannot be cured
   ii. Stress can trigger psoriasis
   iii. Psoriasis is contagious
   iv. Psoriasis can be associated with arthritis
   A. (i) and (ii) only
   B. (i), (ii) and (iii) only
   C. (i), (ii) and (iv) only
   D. (ii), (iii) and (iv) only

4. ***Which of the following types of psoriasis is characterized by small salmon-pink papules (1-10 mm in diameter) predominantly on the trunk?***
   A. Erythrodermic psoriasis
   B. Plaque psoriasis
   C. Pustular psoriasis
   D. Guttate psoriasis

5. ***Which of the following about phototherapy is INCORRECT?***
   A. Excimer laser is particularly useful for treating psoriasis plaques that are located in difficult areas such as scalp, palms, knees, elbows and soles
   B. Narrowband UVB are more commonly used than broadband UVB due to greater efficacy, longer duration of remission, lower photocarcinogenic potential and less erythema
   C. PUVA is the most efficient phototherapy and hence most commonly used to treat moderate to severe psoriasis
   D. In general, phototherapy is contraindicated in patients with a history of melanoma or extensive non-melanoma skin cancer

6. ***Which of the following statement regarding the treatment of psoriasis is TRUE?***
   A. There is a risk of exacerbation of infection when topical corticosteroids is applied to infected psoriatic skin
   B. Combined use of calcipotriol and potent corticosteroids is not recommended to treat psoriasis
   C. Super potent corticosteroids are used to treat psoriasis on the face and groin areas
   D. Tazarotene is a topical calcineurin inhibitor used to treat psoriasis

7. ***Which of the following statement regarding systemic treatment for psoriasis is INCORRECT?***
   A. Cyclosporin exerts it immunosuppressive effect through inhibiting the production of IL-2
   B. Acitretin belongs to the derivatives of vitamin A
   C. Methotrexate is a folic acid antagonist that is available in both oral and subcutaneous form of administration
   D. Methotrexate should not be used long term due to its potential adverse effects

8. ***Which of the following statement regarding biologics treatment for psoriasis is TRUE?***
   i. Etanercept was the first TNF-α inhibitor approved by the FDA for psoriasis
   ii. Ustekinumab is the only biologic that inhibits both IL-12 and IL-23 through inhibition of their shared p40 subunit
   iii. Ixekizumab attenuates an inflammatory response mediated by IL-17A and disrupts the pathogenic inflammatory cascade of psoriasis
   iv. Risankizumab is one of the newest IL-23 inhibitor to date approved by the FDA for the treatment of moderate to severe psoriasis
   A. (i) and (ii) only
   B. (ii) and (iii) only
   C. (i), (ii) and (iv) only
   D. All of the above

9. ***Which of the following biologics is approved for use during pregnancy and breastfeeding?***
   A. Etanercept
   B. Certolizumab
   C. Secukinumab
   D. Guselkumab

10. ***Which of the following statement is INCORRECT?***
    A. Secukinumab has established its efficacy and safety through ERASURE and FIXTURE trials
    B. Ustekinumab has established its efficacy and safety through PHOENIX-1 and PHOENIX-2 trials
    C. Brodalumab has established its efficacy and safety through AMAGINE-2 and AMAGINE-3 trials
    D. Tildrakizumab has established its efficacy and safety through VOYAGE-1 and VOYAGE-2 trials

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 293(D&T)

COVID-19: Update on Evidence for a Pre-Exposure Prophylaxis Strategy versus Post-Exposure Prophylaxis

1. D 2. A 3. D 4. C 5. C 6. D 7. C 8. B 9. B 10. C

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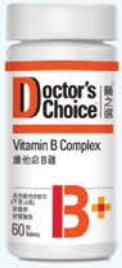

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The Activities of the Society of Hospital Pharmacists

Hi fellow pharmacists, as we step into 2023, we are proud to say that we have finally overcome the challenges posed by the COVID-19 pandemic. It has been a tough journey, but with everyone's effort and professionalism, we've made it through together.

In the past few months, the Society of Hospital Pharmacists of Hong Kong (SHPHK) has collaborated with three other organizations to organize several online webinar lectures as a way to connect with our members. Despite the limitation of virtual lectures, the webinars have been supported by numerous pharmacists. With the border opened and the dropping of the mask mandate, we are looking forward to have more physical meetings including local lectures and overseas conference in the coming months.

Webinar on ambulatory care pharmacist clinic

SHPHK has collaborated with the University of Hong Kong (HKU) Department of Pharmacology and Pharmacy to hold a webinar "Ambulatory Care Clinic Pharmacist Practice - Understanding the Local Landscape" on 4th February, 2023. Ambulatory care pharmacist clinic is currently in the development plan of Hospital Authority (HA). In the webinar, we have invited six experienced clinical pharmacists from multiple HA hospitals to share their skills in the setup of ambulatory clinics including drug refill service, diabetes clinic, oncology clinic, anticoagulation clinic and heart failure clinic. The event has attracted over 100 pharmacists, interns, and pharmacy students to attend.

Webinar on "Brand versus Generic medications in Psychiatry"

On 17th March, 2023, SHPHK collaborated with the Hong Kong College of Psychiatrists in organizing the second webinar "Brand versus Generic Medications in Psychiatry". We are honoured to have Dr Howard C. Margolese, associate professor of the Department of Psychiatry, McGill University as the guest speaker. Generic mediations have been commonly used as an alternative therapeutic option to reduce drug cost. However, it may not provide therapeutic equivalence when applying on psychiatric patients leading to treatment failure or additional side effects. Dr Margolese has provided insights and practical knowledge on the use of generic medications in psychiatric practice. This webinar has attracted an attendance of 268 people, including pharmacists and psychiatrists from Hong Kong and Asian countries.

Webinar on physician-pharmacist collaborative anticoagulation clinic

Just one week after the last webinar, SHPHK collaborated with the College of Pharmacy Practice (CPP) to hold the third webinar "Ambulatory Care Service: Physician-Pharmacist Collaborative Anticoagulation Clinic" on 22nd March, 2023. The webinar has invited Ms. Yoyo Wong, pharmacist at Tuen Mun Hospital, and Dr. Ha Chung Yin, associate consultant at Tuen Mun Hospital, as speakers. Pharmacist anticoagulation clinic (PAC) has been started in Tuen Mun Hospital since September 2019. The clinic further expanded to include two full time pharmacists

to deliver service since October 2022. The webinar introduced an interdisciplinary care approach in running the PAC. They delivered the service by monitoring patient's anticoagulation control by adjusting warfarin dosage, assess and evaluate factors which have impact on patient's anticoagulation control.

If you have missed any of the above webinars and you are a member of SHPHK, you can always visit SHPHK homepage and sign in to view all the past webinar recordings (shphk.org.hk > resources > learning activities)

第二屆滬港澳臺醫院藥學管理高峰論壇

With the abolishment of all social distancing measures, we are thrilled to introduce you this exciting event to be taken place in Shanghai from 27th to 29th May 2023. SHPHK has participated in the first 滬港醫院藥學管理高峰論壇 in November 2019 in Shenzhen. Unfortunately due to COVID-19 pandemic, the second conference didn't happen in the past few years. By 2023, the second conference is finally confirmed to be held in Shanghai again. This year will focus on "Working together to look into the future - Supporting the development of high-quality pharmacy". The conference will feature speakers from Mainland, Hong Kong, Macao and Taiwan to share their experiences and insights to uphold the standard of pharmacy practice during and post COVID-19 pandemic.

SHPHK is excited to be invited by the organizer again to take part in the conference. We are happy to have Ms Chiang Sau Chu, Director of Pharmaceutical Care Foundation (PCF) and Drug Education and Resources Centre (DERC) and Ms Zoey Tsui, pharmacist of Hong Kong Sanatorium Hospital and General Committee member of SHPHK to represent Hong Kong to speak at the conference. This is a great opportunity for our members to learn from experts and network with colleagues from various regions. SHPHK will send a maximum of 10 members to participate in the conference physically in Shanghai. Hospital pharmacy visit will also be arranged after the conference in Shanghai. Stay with us and we hope to share with you our insights gained from this conference in the next issue.

You are most welcome to follow the Society's Facebook page (@SHPHK) and Instagram (@SHPHK1987) to know more about the Society's development and activities. You may also visit the Drug Education Resources Centre (DERC) Website: www.derc.org.hk to keep abreast of the latest news and development of pharmaceutical services in Hong Kong. Join us now as new member or renew your membership at the Society's website: www.shphk.org.hk.

The Activities of the Pharmaceutical Society of Hong Kong

Social Event —「愛老敬老」慶回歸2022

PSHK was invited to join the event "「愛老敬老」慶回歸2022" on 7th January 2023. This social event was organised by Building Healthy Kowloon City Association Limited and co-organised by Home Affairs Department Kowloon City District Office. As one of the supporting organisations, PSHK's pharmacist members provided volunteer medication screening and medication reconciliation for elderly who lived in Kowloon City District.

Pharmacist Volunteers were providing volunteer medication screening and medication reconciliation for elderly

CUHK Visit with FIP Immediate Past President

Mr. Robert Moss, the Immediate Past President of FIP Hospital Pharmacy Section, visited Hong Kong. As a FIP organisation member, PSHK sent our representatives, Mr. Dick Sung, Mr. Rex Ng and Mr. Patrick Tam to join his visit to the School of Pharmacy, CUHK with CUHK representatives on 4th April 2023.

PSHK would like to express our gratitude to the Director and Professor of CUHK School of Pharmacy, Professor Joan Zuo, for her kind arrangement of Mr. Robert Moss's visit to CUHK.

Group photo of Mr. Robert Moss, FIP Immediate Past President, PSHK and CUHK representatives.

Attend the Conference – 「2023海峽兩岸醫院藥學大會暨海醫會醫院藥學專委會第五屆」

「2023海峽兩岸醫院藥學大會暨海醫會醫院藥學專委會第五屆」was grandly held in Haikou (capital city of Hainan Province), on 24th-26th March 2023. The conference was hosted by Cross-Straits Medicine Exchange Association (海峽兩岸醫藥衛生交流協會); co-hosted by Taiwan Society of Health-System Pharmacists, The Pharmaceutical Society of Hong Kong and The Pharmaceutical Society of Macao; and co-organised by Hainan Pharmaceutical Association and Hainan General Hospital. A total of more than 700 pharmaceutical experts, scholars and pharmacists from cross-straits, Hong Kong and Macau attended the conference.

As one of the co-host organisations, PSHK sent 6 representatives to attend the event. Experts shared and exchanged their views and opinions on different topics, which included: smart pharmacy and innovative services, individualisation of drug therapy, chronic disease management and pharmacy services, research and practice of clinical pharmacy as well as rational use of traditional Chinese medicine and so on.

It was a fruitful event for our representatives to learn the pharmacy development in Mainland, Taiwan and Macau; and to connect with their local experts.

The group photo of the guests.

PSHK President, Mr. Dick Sung was sharing on the topic of "Hong Kong Primary Health Blueprint – Sharing on the model of Pharmaceutical Services"

Hong Kong Pharmaceutical Journal: For Detailed Instructions for Authors

INTRODUCTION

Hong Kong Pharmaceutical Journal (HKPJ) is the official publication of the Pharmaceutical Society of Hong Kong, the Practising Pharmacists Association of Hong Kong and the Society of Hospital Pharmacists of Hong Kong. It is a journal of the pharmacists, for the pharmacists and by the pharmacists. The Journal is currently divided into several sections: ***Editorial Comment; News & Short Communications; Pharmacy Practice; Over-the-Counter & Health; Drugs & Therapeutics; Primary Care; Herbal Medicines & Nutraceuticals; Pharmaceutical Technology*** and ***New Products***. It publishes review articles or original papers relevant to these different fields of pharmacy. In addition to the regular three issues of the Journal per year, there are issues dedicated solely to reports on special function of the society. The Aims and Scope of the Journal are published on the inside back cover of each issue.

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