MADRAC Bulletin

for healthcare professionals only
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The MADRAC Bulletin is a bi-monthly publication that provides a selection of local safety signals and articles discussing local individual case safety reports (ICSRs) meant to raise awareness among healthcare professionals.

The MADRAC Bulletin also features pharmacovigilance-related activities conducted by the National Pharmaceutical Regulatory Agency (NPRA) and contains a list of directives based on safety issues advised by the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) and endorsed by the Drug Control Authority (DCA) as well as safety alerts that have been published on the NPRA website.

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We would like to thank the Director General of Health, Malaysia for his permission to publish the case report articles.

Articles Based on Case Reports

This section discusses local individual case safety reports of suspected adverse events recorded in the Malaysian Pharmacovigilance Database (QUEST).[1] The case reports presented in this section are intended to serve as a reminder of potential adverse events that healthcare providers should be aware of in day-to-day clinical practice, take account of, and report to the NPRA if any relevant events occur. Information contained in these articles is not comprehensive but rather represents a selection of clinically relevant items that warrants dissemination.

Dacomitinib: Local Case Reports on Palmar-Plantar Erythrodysesthesia Syndrome (PPES)

By Goh Pui Yen

Case Report 1[1]

A 59-year-old male patient was prescribed dacomitinib 30 mg once daily for the treatment of non-small cell lung cancer (NSCLC). Five months after therapy initiation, the patient presented during a regular follow-up with new complaints and was diagnosed with **Grade 3 palmar-plantar erythrodysaesthesia syndrome (PPES)** and paronychia (infection of the skin around the nails). The dosage of dacomitinib was subsequently reduced to 30 mg every other day. On subsequent follow-ups, the adverse events (AEs) improved to **Grade 1 PPES** and paronychia. Given the improvement, the dacomitinib dosage was reoptimised to 30 mg once daily. Considering the potential presence of confounding factors during the extended time-to-onset, the observed PPES was assessed as *possibly* related to dacomitinib.

Case Report 2[1]

An 80-year-old female patient took dacomitinib 30 mg once daily for the treatment of NSCLC. Four months after starting the therapy, the patient developed **PPES** and paronychia. She was prescribed fusidic acid / hydrocortisone acetate cream and aqueous cream for the treatment of the abrasion wound over her finger, and ketoconazole cream for paronychia. Dacomitinib treatment was temporarily withheld, and resumed after the symptoms improved on Day 18. Due to the use of concomitant drugs, the observed PPES was assigned a *possible* relation to dacomitinib.

Discussion

Dacomitinib is a second-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) that irreversibly inhibits the kinase activity of the human EGFR family and certain EGFR activating mutations (exon 19 deletion or the exon 21 L858R substitution mutation).[2-4] In Malaysia, there is only one registered product containing dacomitinib, which is indicated for the first-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations.[4,5]

Dacomitinib, has been associated with dermatologic adverse events, including **palmar-plantar erythrodysaesthesia syndrome (PPES).**[4] Compared to reversible EGFR TKIs like gefitinib, the higher incidence of dermatologic adverse events seen with irreversible EGFR TKIs is likely attributable to the covalent bonds formed between irreversible TKIs and EGFR, which prolong the effect of the TKIs.[3,6] The underlying mechanism for dermatologic adverse events involves the inhibition of EGFR in epidermal-derived tissues, where impaired keratinocyte function triggers an inflammatory response, leading to cutaneous injury.[6-7]

PPES, also known as hand-foot skin reaction, is characterised by redness, marked discomfort, swelling and tingling in the palms of the hands or the soles of the feet.[8] The severity of PPES is graded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Common Terminology Criteria for Adverse Events (CTCAE)[8]:

Grade 1: Minimal skin changes or dermatitis *(e.g., erythema, oedema, or hyperkeratosis [thickening of the skin's outer layer])* without pain.

Grade 2: Skin changes with pain; limiting instrumental activities of daily living (ADL) *(e.g., preparing meals, shopping, using the telephone, managing money)*

Grade 3: Severe skin changes with pain; limiting self-care ADL *(e.g., bathing, dressing and undressing, feeding, taking medicines)*.

Clinical studies have reported PPES (all grades) in around 15% of patients treated with dacomitinib.[4,9] The onset of PPES symptoms usually occur within the first four weeks of treatment and may worsen during the subsequent two weeks.[9] Symptoms of PPES often persist for 15 weeks, with severe symptoms lasting about two weeks.

Management of PPES typically involves interruption or dose reduction of dacomitinib depending on the severity of PPES, along with supportive treatment such as topical antibiotics, topical steroids, emollients, keratolytics, and analgesics.[9,10] Predisposing factors, such as apparent hyperkeratosis, should be addressed prior to initiating dacomitinib treatment.[10] General preventive measures include using alcohol-free skin moisturisers, avoiding irritation to the hands and feet (e.g., tight-fitting shoes or long walks), minimising chemical stress (e.g., skin irritants), and using protective clothing and sunscreen when exposed to sunlight.[4,9,10]

To date, NPRA has received **86 adverse drug reaction (ADR) reports** with 194 adverse events suspected to be related to dacomitinib.[1] The most frequently reported adverse events include diarrhoea (20 cases), paronychia (16), and rash (13). **Seven cases of PPES** involving dacomitinib have been reported in Malaysia, including the two cases discussed in this article.

As of December 2024, a search of the World Health Organisation (WHO) global ADR database[11*] identified a total of 28 cases of PPES suspected to be associated with dacomitinib.

*DISCLAIMER

VigiBase is the WHO global database of reported potential adverse effects of medicinal products, developed and maintained by Uppsala Monitoring Centre (UMC). This information comes from a variety of sources, and the likelihood that the suspected adverse effect is drug-related is not the same in all cases. This information does not represent the opinion of the UMC or the WHO.

Advice for Healthcare Professionals

1. Be aware that PPES, also known as hand-foot skin reaction, has been associated with dacomitinib treatment.
2. Evaluate and address predisposing factors, such as apparent hyperkeratosis, before initiating dacomitinib treatment, to reduce the likelihood of PPES.
3. Counsel patients and caregivers on preventive care measures for PPES. Advise patients to report early symptoms of PPES, such as redness, tingling, or discomfort in the palms or soles, to medical personnel for timely intervention.
4. When PPES is suspected, assess its severity and adjust dacomitinib treatment as necessary, along with supportive management.
5. Report all suspected adverse events associated with dacomitinib-containing products to the NPRA.

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Dupilumab-Induced Arthralgia

By Ng Wan Ning

Case Report 1 [1]

A 52-year-old female was prescribed subcutaneous (sc) dupilumab 300 mg every other week for the treatment of severe asthma. One hour after the first dose of dupilumab, the patient developed **joint pain** and muscle pain. She was treated with paracetamol and recovered within 2 weeks of the reaction onset. Considering the potential presence of concomitant drugs, given that dupilumab is generally indicated as an add-on therapy for severe asthma management[2], the drug-reaction causal relationship for this case was assessed as *possible*.

Case Report 2 [1]

A 57-year-old male patient received sc dupilumab 300 mg every other week for the treatment of severe asthma. Approximately 2 hours after the 6th dose of dupilumab, he developed **bilateral wrist and ankle pain accompanied by bilateral foot swelling**. The symptoms were managed with mefenamic acid (TDS/PRN) and paracetamol (1g QID), and the patient recovered within 1 week. Following the administration of the 7th dose of dupilumab, the patient again experienced **ankle pain** approximately 2 hour post-injection. He was prescribed analgesics and recovered within 2 weeks.

Considering the potential presence of confounding factors over an extended period and the use of concomitant drugs, the causal relationship between the drug and the observed event in this case was assessed as *possible*.

Discussion

Dupilumab is a human monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signalling by binding to the interleukin-4 receptor alpha subunit (IL-4Rα), thereby reducing inflammatory conditions associated with these interleukins.[2] It is indicated for the treatment of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and prurigo nodularis. In Malaysia, there are two registered products containing dupilumab, both available as injections.[3]

Arthralgia, defined as pain in any joint of the body, has been reported in patients using dupilumab for atopic dermatitis, asthma, and CRSwNP, based on clinical trials, literature case series, and post-marketing reports.[2,4-6] Affected joints varied among individuals, were generally bilateral, and included the hands, shoulders, wrists, hips, neck, knees, or ankles.[4,6] Associated symptoms included swelling, stiffness, tenderness, radiating pain, and achiness.

The mechanism behind dupilumab-induced arthralgia is not fully understood, but several hypotheses have been proposed. By blocking the IL-4/IL-13 axis, dupilumab may hinder its protective role against the IL-23/IL-17 axis, which is associated with various inflammatory conditions, thereby predisposing individuals to joint inflammation and pain.[5,7] Another hypothesis suggests that reduced IL-4 levels may increase the production of pro-inflammatory cytokines, such as TNF-α and IL-6, further promoting joint-related symptoms.[4,5]

Dupilumab-induced arthralgia has been reported to occur at varying intervals, ranging from days to over a year after treatment initiation.[2,4-6] Some patients reported gait disturbances, impaired mobility, and exercise limitations, with a few requiring hospitalisation.[2,6] In some cases, symptoms resolved during continued treatment while being managed with analgesics like NSAIDs and corticosteroids. Other cases recovered or were recovering following discontinuation of dupilumab.

To date, the NPRA has received **91 adverse drug reaction reports** with 168 adverse events associated with dupilumab use.[1] The most frequently reported adverse events were conjunctivitis (17 cases), erythema (10), and eczema (10). **Five cases of arthralgia** (including the 2 cases described above) were reported, affecting 3 females, 1 male, and 1 patient of unspecified gender. The reported time to onset of arthralgia ranged from hours to 3 days. Four patients recovered from the adverse event, while 1 reported an unknown outcome.

Globally, based on the WHO database as of December 2024, there were a total of 283,335 adverse events reported in association with dupilumab use.[8]* Of these, 11,471 cases reported arthralgia.

DISCLAIMER

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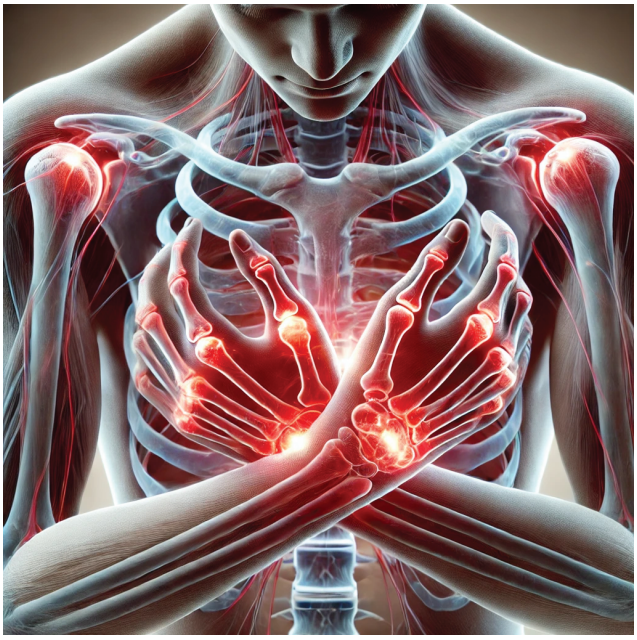
Advice for Healthcare Professionals

1. Be aware of the risk of arthralgia associated with dupilumab, which may occur from days to over a year after treatment initiation.

2. Educate patients to report any new or worsening joint symptoms to their healthcare provider.

3. If the patient presents with arthralgia:
   - Assess its severity and engage in shared decision-making with the patient.
   - Consider continuing dupilumab treatment if benefits outweigh risks, while managing symptoms with appropriate pharmacological options.
   - If joint symptoms persist or worsen, consider a rheumatological evaluation and/or discontinuation of dupilumab.

4. Report any adverse drug reactions suspected to be related to dupilumab use to the NPRA



*AI-generated image

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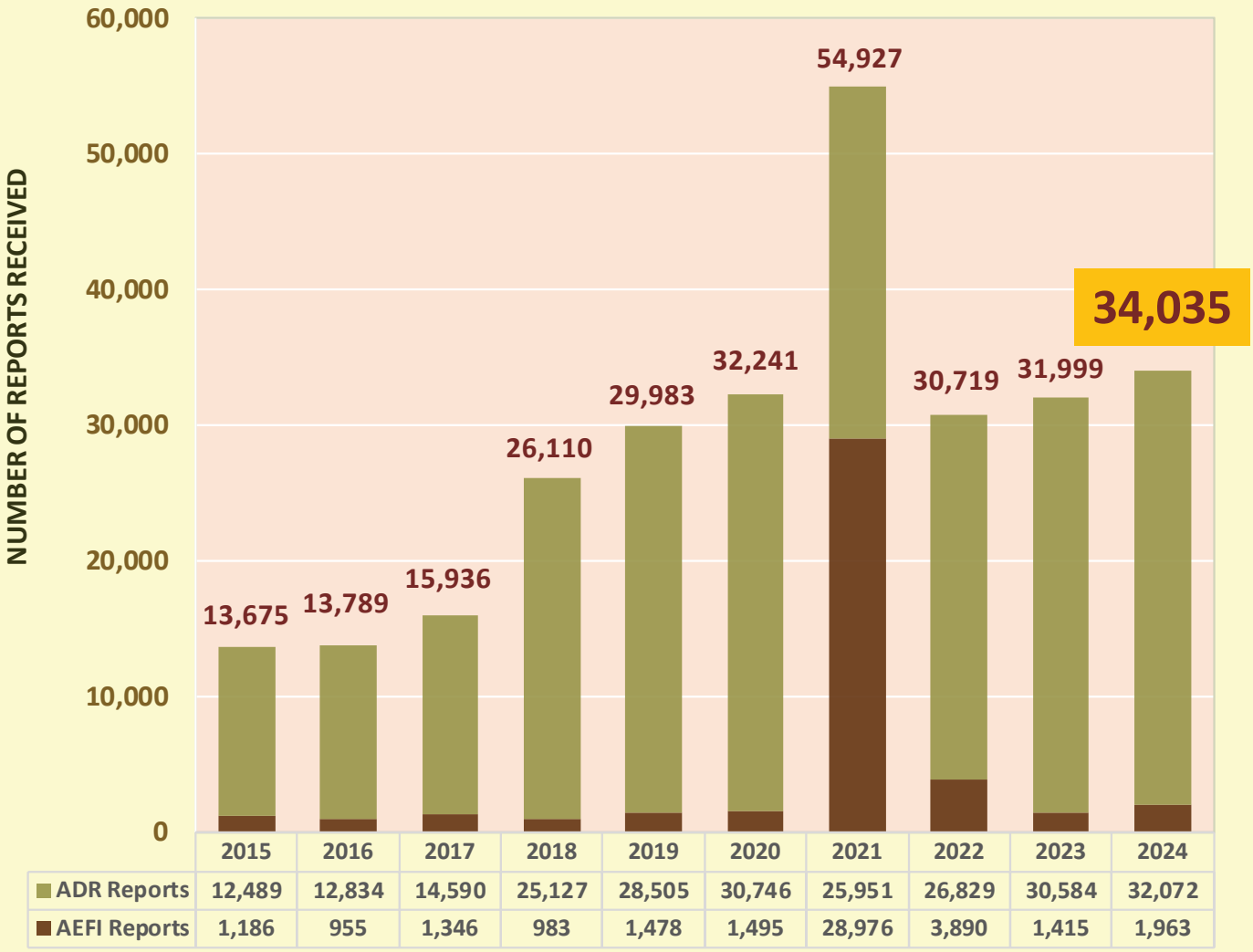
Features

Adverse Event Reports Received 2015-2024

In 2024, the NPRA received a total of **34,035** adverse drug reaction (ADR) and adverse event following immunisation (AEFI) reports from across Malaysia, marking a 6.4% increase from the 31,999 reports recorded in 2023 (***Figure 1***).



	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
ADR Reports	12,489	12,834	14,590	25,127	28,505	30,746	25,951	26,829	30,584	32,072
AEFI Reports	1,186	955	1,346	983	1,478	1,495	28,976	3,890	1,415	1,963

Figure 1. Total Adverse Drug Reaction (ADR) and Adverse Event Following Immunisation (AEFI) Reports Received Annually (2015-2024)

What's New

List of Safety Alerts and Directives Related to Drug Safety Issues

NPRA reviews and presents drug safety issues at meetings of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) to determine the appropriate risk minimisation measures. Regulatory actions are proposed to the Drug Control Authority (DCA), resulting in DCA directives issued to ensure local package inserts and consumer medication information leaflets (RiMUP) for all products containing the affected active ingredients are updated with the required safety information. The table below shows the safety alerts and DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts		Directive Ref. No. [Date]
		Title	Date	
1	Ethambutol	Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	09-Jan-2025	-
2	Glucagon-like Peptide-1 (GLP-1) Receptor Agonists (Dulaglutide, Liraglutide, Lixisenatide, Semaglutide, and Tirzepatide)	Aspiration and Pneumonia Aspiration during General Anaesthesia or Deep Sedation	12-Jan-2025	-

How to report adverse events?

NPRA encourages all healthcare professionals to report all suspected adverse drug reactions (ADR) to medicines, including pharmaceutical products, over-the-counter medicines, traditional medicines, and health supplements, as well as adverse events following immunisation (AEFI) with vaccines.

To report ADR/AEFI:

1. Visit www.npra.gov.my
2. Report ADR as Healthcare Professional
   a) Choose Online Reporting or
   b) Download the ADR manual form and submit the completed form via email or post:

fv@npra.gov.my

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b) send an email with your details to fv@npra.gov.my