MADRAC Bulletin

For healthcare professionals only
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In this issue

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 health care professionals. Information contained in this publication is not comprehensive but rather represents a selection of clinically relevant items warranting enhanced dissemination.

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.

To receive each new issue of this bulletin, complete the subscription form available on the NPRA website.

Signals

Features

What's New

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

Signals

The signals in this Newsletter are based on information derived from reports of suspected adverse events available in the Malaysian Pharmacovigilance Database (QUEST)[1] and the WHO global database of individual case safety reports (VigiBase)[2]. The signals presented below are intended to raise awareness of reported adverse events and stimulate additional reporting from healthcare professionals.*

A safety signal, according to the WHO-Uppsala Monitoring Centre (UMC) definition[3], refers to information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Associated with Antiretroviral Therapy (ART): Efavirenz and Tenofovir/Emtricitabine

Written by Dr Vidhya Hariraj; Reviewed by Nora Ashikin Mohd Ali

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is a type of severe cutaneous adverse reactions (SCARs).[4-6] It is characterised by a generalised exanthematous morbilliform rash, fever, and enlarged lymph nodes, coupled with internal organ involvement (usually the liver and kidneys) and haematologic features (such as leukocytosis with hypereosinophilia). The onset of DRESS syndrome typically occurs 2–8 weeks after taking the offending drug, and the symptoms may prolong for a few weeks or even months upon drug withdrawal. DRESS syndrome has a high mortality rate of around 10%–30%.[5] Patients may also suffer long-term sequelae, either directly from DRESS syndrome-related organ damage or due to treatment-related complications.[6] These include infections following corticosteroid treatment, severe liver damage, and declined kidney function.

Recent local quantitative signal detection analyses on QUEST[1], the national pharmacovigilance database, have detected **two (2) drugs used in antiretroviral therapy (ART)—efavirenz** and a combination of **tenofovir/emtricitabine**—as having a potential association with DRESS syndrome.

Background

ART is the standard treatment for Human Immunodeficiency Virus (HIV) infections.[7] This therapy usually employs three (3) or more antiretroviral (ARV) drugs that target different phases of the HIV life cycle to suppress and manage the virus. ART has been shown to reduce opportunistic infection-related mortality among HIV-infected individuals as well as improve both quality of life and survival.

Efavirenz is a selective non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1).[8] **Tenofovir/emtricitabine** are both classified as nucleoside reverse transcriptase inhibitors (NRTIs).[9] Tenofovir is available in two forms: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), with the newer TAF being a novel prodrug of tenofovir with enhanced plasma stability and intracellular activation.

Signal #1 Efavirenz – DRESS syndrome

Reports in QUEST[1]

As of 31st May 2023, the NPRA had received **25 local reports** of DRESS syndrome associated with efavirenz, indicating a disproportionality value of **IC_{025} = 1.7**. These patients, primarily male (76%), had a mean age of 39 years, ranging from 25 to 64 years. The median time-to-onset was 14 days, with a range of 1–30 days. The majority of these cases (18; 72%) were classified as serious, with an outcome of either recovered or recovering at the time of reporting. All cases were reported by healthcare professionals (doctors/pharmacists) from Ministry of Health hospitals. Causality was assessed as possible in all cases, as each involved at least one (1) co-suspected and/or concomitant drug: **emtricitabine/tenofovir (8 cases),** sulfamethoxazole/trimethoprim (7), lamivudine/zidovudine (5), and dapsone (5).

Reports in VigiBase[2]

As of 31st May 2023, VigiBase recorded **82 global reports** of DRESS syndrome associated with efavirenz, with the disproportionality value standing at **IC_{025} = 1.5**. Thailand reported the highest number of cases (43.9%), followed by Malaysia (30.5%) and India (6.1%). The majority of global cases involved males (59.8%). Co-reported active ingredients included sulfamethoxazole/trimethoprim (13 cases), lamivudine/zidovudine (8), **emtricitabine/tenofovir (7)**, and dapsone (5).

Signal #2 Tenofovir/Emtricitabine – DRESS Syndrome

Reports in QUEST[1]

As of 31st May 2023, the NPRA had received **10 local reports** of DRESS syndrome associated with tenofovir/emtricitabine, exhibiting a disproportionality value of **IC_{025} = 1.5**. These cases reported a time-to-onset ranging from 1 hour to 10 days. The majority of cases (7; 70%) were classified as serious, and most (80%) were recovering at the time of reporting. All cases were reported by healthcare professionals (doctors/pharmacists) from Ministry of Health hospitals. In all cases, the causality was assessed as possible, with each case having at least one (1) co-suspected and/or concomitant drug: **efavirenz (5 cases)**, nevirapine (3), sulfamethoxazole/trimethoprim (2), doxycycline (2), and dapsone (1).

Reports in VigiBase[2]

As of 31st May 2023, the disproportionality value for DRESS syndrome associated with tenofovir/emtricitabine based on global data in VigiBase stood at **IC_{025} = 0.3**. Malaysian reports constituted the second highest proportion, comprising 19.2% of the total 52 reports received worldwide, following France (42.3%). The majority of the reported cases involved males (59.6%), and were aged between 18–44 years. Out of these 52 reports, 49 (94.2%) were categorised as serious. Co-suspected and/or concomitant drugs were similar to the reports recorded in QUEST.

Discussion

Based on the assessment, the currently available evidence is **insufficient to confirm the association between DRESS syndrome and efavirenz or tenofovir/emtricitabine**, due to multiple confounding factors. Both identified signals involved overlapping cases that reported the concurrent use of efavirenz and tenofovir/emtricitabine. Moreover, these signals did not distinguish between the effects of TDF and TAF, both collectively referred to under the umbrella of tenofovir/emtricitabine. In addition, patients undergoing ART might receive other agents to prevent or treat opportunistic infections; these include medications such as sulfamethoxazole/trimethoprim and tuberculostatic drugs, which have a known association with DRESS syndrome.[7]

Despite these confounding factors, it is not possible to entirely refute the signals given the plausible mechanism and the observed time-to-onset of the manifestations of DRESS syndrome. In a cross-sectional Malaysian study, out of 78 people living with HIV (PLWH), efavirenz + tenofovir/emtricitabine were reported as the most common combination (80.6%) associated with cutaneous adverse drug reactions.[10] Furthermore, a systematic review of ART-associated DRESS syndrome in HIV patients found efavirenz to be involved in six (17.1%) out of the 35 examined cases, of which two (2) cases were classified as "probable", three (3) as "possible", and one (1) as a non-DRESS syndrome case.[11]

Notably, drug eruptions are 20 to 100 times more frequent in PLWH than in the general population.[12] The underlying pathogenesis of T-cell-mediated DRESS syndrome is believed to involve a complex interplay of multiple mechanisms.[13-14] These mechanisms include genetic deficiencies in detoxification enzymes resulting in drug metabolite accumulation, genetic associations between specific human leukocyte antigens (HLAs) and susceptibility to drug hypersensitivity, and a potential link between herpes virus reactivation and virus-drug interactions.

*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.

Conclusion & Advice

A signal does not imply a direct causal relationship but serves as a trigger for further investigation to be undertaken. DRESS syndrome is a life-threatening delayed hypersensitivity reaction that is often challenging to diagnose promptly.[4-6,15] Given the complexity of HIV treatment and management with ART, early recognition of DRESS syndrome is essential to prevent undesirable sequelae.

Therefore, healthcare professionals are encouraged to:

- **Be vigilant** for signs and symptoms of DRESS syndrome in HIV patients, especially if symptoms such as lymphadenopathy, eosinophilia, and liver abnormalities develop in the weeks following the initiation of treatments involving efavirenz or tenofovir/emtricitabine.
- **Remind** patients to seek medical assistance immediately if they experience any of the following signs and symptoms: skin reddening, blisters, rash, fever, sore throat, or eye irritation. It is important to further investigate these cases, as the extent and severity of skin involvement may not correlate with the extent of internal organ involvement.
- **Report** any cases of DRESS syndrome suspectedly associated with the use of efavirenz or tenofovir/emtricitabine to the NPRA, mentioning the product brand name where available.

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Features

Publication Carbamazepine-Induced Severe Cutaneous Adverse Drug Reactions: A 21-Year Comparison Between Children and Adults in Malaysia

Vidhya Hariraj , Wee Kee Wo, Sing Chet Lee, Azuana Ramli

Abstract:

Severe cutaneous adverse drug reactions (SCARs) are a life-threatening condition. We aimed to identify all carbamazepine-induced SCARs voluntarily reported to the Malaysian pharmacovigilance database and to compare between children and adults. Adverse drug reaction reports for carbamazepine were extracted from 2000 to 2020, and divided into 2 groups, that is, children (aged 0–17 years) and adults (aged 18 years and above). Age, sex, race, and carbamazepine dose were analyzed using multiple logistic regression. Of 1,102 carbamazepine adverse drug reaction reports, 416 reports were SCARs (99 children, 317 adults). Stevens–Johnson syndrome and toxic epidermal necrolysis were the main SCAR types for both age groups. Median time-to-onset for any type of SCAR was 13 days, regardless of age. In children, Malay individuals were 3.6 times more likely to report SCARs (95% confidence interval, 1.356–9.546; P = .010) compared to the Chinese population. In adults, carbamazepine-induced SCARs were reported as 3.6 times higher in those with a daily dose of 200 mg or less as compared to a daily dose of 400 mg or more. (95% confidence interval, 2.257–5.758; P < .001). Carbamazepine-induced SCARs reported in Malaysia were predominantly Stevens–Johnson syndrome or toxic epidermal necrolysis, with the majority in Malay individuals. Initiation therapy needs close monitoring between 2 weeks and 1 month.

Pharmacovigilance

Carbamazepine-Induced Severe Cutaneous Adverse Drug Reactions: A 21-Year Comparison Between Children and Adults in Malaysia

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Abstract

Severe cutaneous adverse drug reactions (SCARs) are a life-threatening condition. We aimed to identify all carbamazepine-induced SCARs voluntarily reported to the Malaysian pharmacovigilance database and to compare between children and adults. Adverse drug reaction reports for carbamazepine were extracted from 2000 to 2020, and divided into 2 groups, that is, children (aged 0–17 years) and adults (aged 18 years and above). Age, sex, race, and carbamazepine dose were analyzed using multiple logistic regression. Of 1102 carbamazepine adverse drug reaction reports, 416 reports were SCARs (99 children, 317 adults). Stevens-Johnson syndrome and toxic epidermal necrolysis were the main SCAR types for both age groups. Median time-to-onset for any type of SCAR was 13 days, regardless of age. In children, Malay individuals were 3.6 times more likely to report SCARs (95% confidence interval, 1.356–9.546; P = .010) compared to the Chinese population. In adults, carbamazepine-induced SCARs were reported as 3.6 times higher in those with a daily dose of 200 mg or less as compared to a daily dose of 400 mg or more. (95% confidence interval, 2.257–5.758; P < .001) Carbamazepine-induced SCARs reported in Malaysia were predominantly Stevens-Johnson syndrome or toxic epidermal necrolysis, with the majority in Malay individuals. Initiation therapy needs close monitoring between 2 weeks and 1 month.

Keywords

carbamazepine, children, pharmacovigilance, severe cutaneous adverse drug reaction, Stevens-Johnson syndrome

Carbamazepine has been widely used for epilepsy, bipolar disorder, and trigeminal neuralgia since the 1960s. Although effective and generally safe, carbamazepine has been associated with severe cutaneous adverse drug reactions (SCARs).[1] SCARs according to the RegiSCar criteria[2] includes Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Despite being rare, SCARs can result in multiorgan injuries, prolonged hospitalization, and death.[3,4] The only effective intervention in a patient who develops or likely to develop a SCAR is prompt withdrawal and prevention of future use of this medication.

Carbamazepine is the main antiepileptic drug (AED) voluntarily reported for SCARs in the Malaysian pharmacovigilance database at the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health, Malaysia.[5] The national database, established in the year 2000, contains voluntarily submitted adverse drug reaction (ADR) reports received throughout the country from public or private health care facilities, pharmaceutical companies, and consumers. The reports are processed prior to submission to the World Health Organization (WHO) international database (VigiBase).

According to VigiBase, Malaysia is among the top 10 countries with SJS related to carbamazepine.[6] There are many well-documented factors that could play a crucial role in the increased occurrences of ADR such as age, sex, dosing, or preexisting conditions, that is, kidney impairment or liver impairment.[7] Finkelstein et al[8] demonstrated that AEDs were most commonly attributed to causing SJS or SJS/TEN overlap in children.

Previous studies have also demonstrated that carriers of the HLA-B*15:02 allele had a 100-fold risk of developing SJS/TEN with carbamazepine.[9] In countries

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For more information, read the full article published in The Journal of Clinical Pharmacology.

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SCAN HERE

What's New

List of Safety Alerts/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/DCA directives that were recently issued, which are available on the NPRA website.

	Active Ingredients	Safety Alerts (SA)	SA Date	Directive Ref. No. [Date]
1	Third-Generation Aromatase Inhibitors (Anastrozole; Exemestane; Letrozole)	Risk of Tendon Disorders	02-Aug-2023	-
2	Clindamycin (Systemic)	[Updated] Risk of Acute Kidney Injury	07-Aug-2023	NPRA.600-1/9/13 (26) Jld.1 [11 Jul 2023]
3	Valaciclovir	Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	23-Aug-2023	NPRA.600-1/9/13 (24) Jld.1 [11 Apr 2023]
4	Cephalosporins	Risk of Seizures	05-Sep-2023	-

How to report adverse events?

NPRA encourages all health care 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 Health Care 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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NPRA Safety Information Mailing List

To join the mailing list, complete the **subscription form** available on NPRA website, or send an email with your details to **fv@npra.gov.my**