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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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AE Case in Focus: Test Yourself

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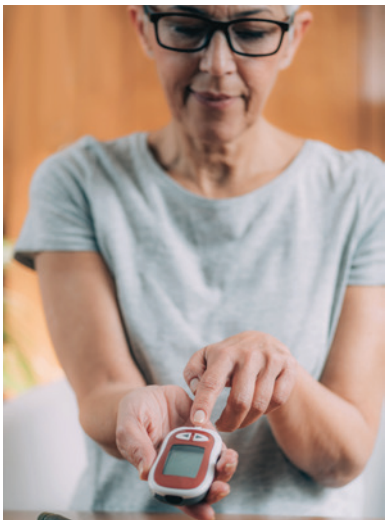
This is a case of a 70-year-old female with hypertension and type 2 diabetes mellitus who was admitted to the hospital with community-acquired pneumonia. She presented with a fever, cough, nausea and loss of appetite of one week's duration. Her HbA1c was 7.6% (60 mmol/mol) on admission. Her medications included metformin, empagliflozin (which she continued taking prior to admission) and losartan. Investigations revealed a high anion gap metabolic acidosis, with raised ketones measuring 3.7 mmol/L. Her plasma lactate was normal. Serum glucose was not significantly raised at 11.0 mmol/L. She was diagnosed with euglycaemic diabetic ketoacidosis (eDKA) and treated with intravenous (IV) insulin infusion, fluid replacement and antibiotics for her pneumonia. Her anti-glutamic acid decarboxylase antibodies and anti-islet cell antibodies were negative.



What could have contributed to her euglycaemic DKA?

HSA-approved educational materials for healthcare professionals

We wish to highlight that soft copies of HSA-approved educational materials for healthcare professionals and their patients are available on the HSA website (www.hsa.gov.sg/educational-materials-for-HCP). They include Physician Educational Materials (PEM), Patient Medication Guides (PMG) and Patient Alert Cards (PAC). These materials are developed by pharmaceutical companies and reviewed by HSA as part of the risk management plan. They highlight important safety concerns associated with selected medicinal products to assure their safe use. Educational materials reviewed by HSA can be identified by this printed statement, "This document has been approved by HSA on <Date>".

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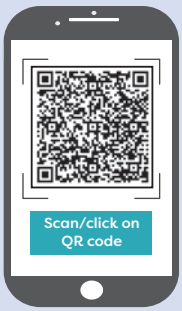
Dear Healthcare Professional Letters on safety concerns



Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

How to report suspected AEs to HSA?

For any suspected AEs, please report to us via the following:

HSA_productsafety@hsa.gov.sg

https://www.hsa.gov.sg/adverse-events

For any enquiries or assistance on AE reporting, please call us at 6866 1111

All website references were last accessed on 1 Dec 2024.

Potential risk of psychiatric withdrawal events with domperidone for stimulation of lactation

Key Points

- A small number of overseas cases of psychiatric withdrawal events have been reported with domperidone when used off-label for stimulation of lactation. In most of these cases, the patients had been taking daily doses greater than 30 mg and for longer than four weeks prior to the sudden discontinuation or tapering attempt.
- HSA has not received any local adverse event report of psychiatric withdrawal events following domperidone use in lactation stimulation from healthcare professionals, although a single medically unverified consumer report was received.
- Healthcare professionals may wish to consider the information related to the reported cases of psychiatric withdrawal events in their management of patients prescribed with domperidone for stimulation of lactation.

Domperidone is a selective dopamine receptor antagonist approved locally for the treatment of delayed gastric emptying, gastro-oesophageal reflux, oesophagitis, nausea and vomiting. The approved recommended dose for adults is 30 mg/day, which can be increased to a maximum of 40 mg/day. The maximum treatment duration generally ranges from one to four weeks depending on the indication but may be extended upon re-assessment of the patient's need for continued treatment.

Domperidone has also been used off-label to promote lactation when deemed medically necessary by doctors. The prescribed dose and duration of treatment is based on the assessment of the individual patient's situation. Domperidone-containing products have been registered in Singapore since 1989 and there are currently nine products registered.

Overseas reports of psychiatric withdrawal events with domperidone for stimulation of lactation

A small number of cases of psychiatric adverse events following sudden discontinuation or tapering of domperidone for stimulation of lactation have been reported overseas. These included nine cases identified by Health Canada and six cases by the US Food and Drug Administration (FDA).[1,2] These cases reported various adverse events such as agitation, anxiety, confusion, depression and insomnia. In most of these cases, the patients had been taking daily doses greater than 30 mg and for longer than four weeks prior to the sudden discontinuation or tapering attempt.

It should be noted that the number of cases is small, and the onset of psychiatric symptoms could be independently associated with the cessation of breastfeeding or the emotional distress resulting from lactation difficulties, rather than being directly linked to domperidone discontinuation. These limit the assessment of a causal relationship between domperidone withdrawal and the reported psychiatric events. Nevertheless, there is a biological plausibility for the association. One postulated mechanism involves the abrupt decrease in plasma prolactin levels, which follows prolonged hyperprolactinaemia induced by long-term domperidone treatment.[3] This could produce a sudden rise in dopaminergic activity and precipitate dopamine-mediated psychiatric events. Another hypothesis is that the higher doses of domperidone used for stimulation of lactation may result in significant penetration of the blood-brain-barrier, which is not generally associated with on-label doses.[4]

Local situation

As at 31 October 2024, HSA has not received any local adverse event report of psychiatric withdrawal events following domperidone use in stimulation of lactation from healthcare professionals. However, there was one medically unverified report from a consumer who reported that she experienced psychiatric events (including anxiety and depression) upon discontinuation of domperidone which was prescribed after her delivery to help with breastfeeding. The dose and duration of domperidone prescribed was not provided and it was noted that she had a medical history of depression before pregnancy.

HSA's advisory

Healthcare professionals may wish to consider the above information in their management of patients prescribed with domperidone for stimulation of lactation. They are also encouraged to report suspected serious adverse events related to domperidone to the Vigilance and Compliance Branch of HSA.

References

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AE Case in Focus: Test Yourself

A 70-year-old female with hypertension and type 2 diabetes mellitus was admitted to the hospital with community-acquired pneumonia. She presented with a fever, cough, nausea and loss of appetite of one week's duration. Her HbA1c was 7.6% (60 mmol/mol) on admission. Her medications included:

- metformin 1000 mg twice a day
- empagliflozin 25 mg every morning (which she continued taking prior to admission)
- losartan 100 mg every morning

Further investigations revealed a high anion gap metabolic acidosis, with raised ketones measuring 3.7 mmol/L. Her plasma lactate was normal. Serum glucose was not significantly raised at 11.0 mmol/L. She was diagnosed with euglycaemic diabetic ketoacidosis (eDKA) and was initiated on intravenous (IV) insulin infusion, fluid replacement and antibiotics (for pneumonia). Empagliflozin was stopped. When her eDKA resolved, she was transitioned to the following for diabetes management:

- subcutaneous Lantus® (insulin glargine) 6u every morning
- metformin 1000 mg twice a day
- sitagliptin 100 mg every morning

Her anti-glutamic acid decarboxylase antibodies and anti-islet cell antibodies were negative.

Q: What could have contributed to her euglycaemic DKA?

HSA would like to thank Dr Elaine Chua Jia Min, Consultant, from the Department of Endocrinology at the Sengkang General Hospital for contributing this article.

Answers can be found on page 6.

Overview of serious adverse event reports associated with programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors

Key Points

- PD-1 and PD-L1 immune checkpoint inhibitors are associated with serious immune-related adverse events (AEs) that may be unpredictable in terms of onset, severity and type.
- Some of the serious AEs of interest known to be associated with these therapies include Stevens-Johnson syndrome, toxic epidermal necrolysis, pneumonitis, colitis and thyroid dysfunction.
- Healthcare professionals are encouraged to report serious AEs suspected with the use of PD-1 and PD-L1 inhibitors to HSA.

Cancer immunotherapies have changed the landscape of cancer treatment in the last few decades. Among these, programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) immune checkpoint inhibitors (ICIs) are increasingly used for different types of cancers.[1] This review article provides an overview of serious adverse events (AEs) reported locally with the use of PD-1 and PD-L1 inhibitors in the last ten years and an analysis of some serious AEs of interest. It also aims to educate healthcare professionals on these serious AEs associated with this class of drugs and encourage reporting of those assessed as CTCAE[#] grade 3 and above to HSA.

[#] A set of standardised definitions for adverse events called Common Terminology Criteria for Adverse Events (CTCAE) to describe the severity of organ toxicity in patients receiving cancer therapy: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

PD-1 and PD-L1 immune checkpoint inhibitors

PD-1 and PD-L1 inhibitors work by blocking the receptors on immune cells (e.g., T-cells) and ligands on tissue cells (e.g., cancer cells) respectively, preventing them from binding to each other. This releases the 'brakes' of the T-cells, allowing the T-cells to recognise and attack cancer cells.[2] In 2015, HSA approved its first ICI targeting PD-1 in Singapore. Six other PD-1 and PD-L1 inhibitors were approved from 2016 to September 2024 (refer to Table 1).

Table 1. Approved PD-1 and PD-L1 immune checkpoint inhibitors in Singapore

Drug (Brand)	Target	HSA approval	Approved indication(s)
Pembrolizumab (Keytruda®)	Programmed cell death 1 (PD-1)	October 2015	Melanoma, non-small cell lung carcinoma (NSCLC), head and neck cancer, classical Hodgkin lymphoma (CHL), urothelial carcinoma, gastric cancer, oesophageal cancer, colorectal cancer, hepatocellular carcinoma (HCC), cervical cancer, renal cell carcinoma (RCC), endometrial cancer, triple-negative breast cancer
Nivolumab (Opdivo®)		April 2016	Melanoma, NSCLC, malignant pleural mesothelioma, RCC, CHL, squamous cell cancer of the head and neck, gastric/gastroesophageal cancer, oesophageal squamous cell carcinoma, gastroesophageal junction cancer, urothelial carcinoma
Dostarlimab (Jemperli)		October 2022	Endometrial cancer
Tislelizumab (Tevimbra®)		September 2024	Locally advanced NSCLC, metastatic NSCLC, oesophageal squamous cell carcinoma
Atezolizumab (Tecentriq®)	Programmed cell death ligand 1 (PD-L1)	February 2018	Early-stage NSCLC, metastatic NSCLC, small cell lung cancer (SCLC), triple-negative breast cancer, HCC
Durvalumab (Imfinzi®)		October 2018	Locally advanced NSCLC, SCLC, biliary tract cancer, HCC
Avelumab (Bravencio)		April 2019	Metastatic Merkel cell carcinoma, locally advanced metastatic urothelial carcinoma, advanced RCC

With the growing use of PD-1/PD-L1 inhibitors, HSA has also received more serious[#] AE reports associated with this class of products (Figure 1). The majority of these AEs are immune-related, which differ from those of traditional cytotoxic chemotherapy. These AEs typically have a delayed onset, prolonged duration and can potentially involve any organ or system in the body. Although these AEs are generally treatable and reversible, there are some which are life-threatening or may lead to permanent disorders.[1] Despite more serious AEs reported to HSA, the benefit-risk profile of these drugs remain favourable.

[#] A serious AE corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect or any other important medical events.

Report analysis (till 30 September 2024)

a) Volume of reports

As at 30 September 2024, HSA received a total of 605 valid* AE reports associated with PD-1 and PD-L1 inhibitors, of which 321 reports (53.6%) were assessed as serious. Refer to Figure 1 for the trending of the number of serious AE reports from December 2015 – September 2024.

**Reports lacking important details such as names of suspected drugs and AE descriptions were regarded as invalid reports and were not captured into the national AE database as they could not be assessed for causality. One AE report may be associated with more than one PD-1 and/or PD-L1 inhibitors.*

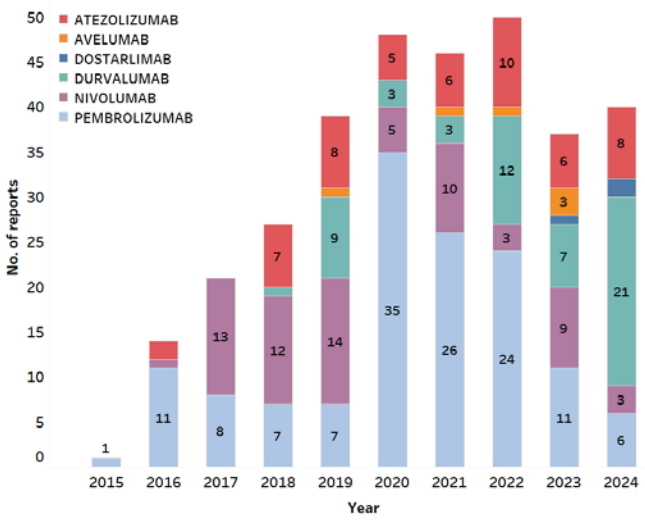

Figure 1. Local reports of serious adverse events with PD-1 and PD-L1 ICIs received by HSA in the last ten years (December 2015 – September 2024)

b) Demographics

Where patient demographics were reported, there were more AEs reported in males (59%) than in females (33%). Majority of the reports did not include ethnicity but among those reported, Chinese patients constituted the highest proportion (17.6%), followed by Malays (1.2%), Caucasians (0.6%), Indians (0.3%) and Eurasians (0.3%).

In Singapore, majority of patients with cancer are in the older age group (50 years and above).[3] Therefore, most patients reported in the AE reports were also in the higher age range. The patients' age range with the highest reported frequency was 60 - 69 years of age (31.2%), followed by 70 - 79 years (21.6%), 50 - 59 years (14.8%) and 40 - 49 years (5.9%) (Figure 2).

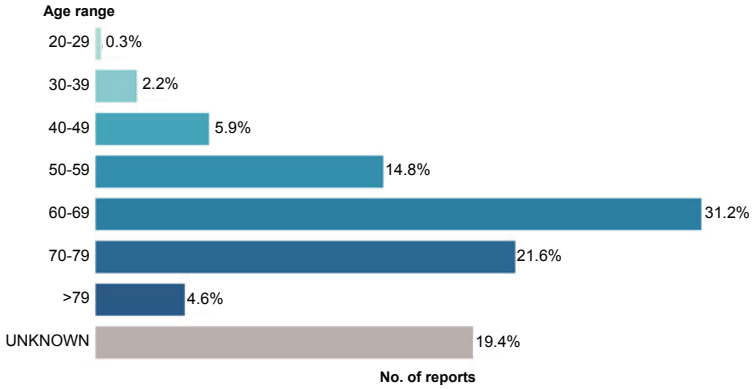

Figure 2. Distribution of age ranges of patients

c) Types of serious AEs reported

A large proportion of serious AEs reported were respiratory disorders (11.8%), cutaneous disorders (10%), gastrointestinal disorders (6%), and endocrine disorders (3.5%). It is worth noting that more than one AE may be mentioned in a single AE report and that these figures do not take into consideration the drugs' utilisation rates and hence do not inform on their relative safety profiles. Table 2 provides further breakdown of some known serious AEs of interest for each PD-1 and PD-L1 inhibitors.

Table 2. Number of reports received for each PD-1 and PD-L1 inhibitor for serious AEs of interest

Drug (Brand)	Serious adverse events (number of reports) by System Organ Class (SOC)			
	Respiratory disorders	Cutaneous disorders	Gastrointestinal disorders	Endocrine disorders
Pembrolizumab (Keytruda®)	Pneumonitis (9), pneumonia (14), pleural effusion (1)	Stevens-Johnson syndrome (SJS) (9), Toxic epidermal necrolysis (TEN) (6)	Colitis (1), duodenitis (1), enteritis (1), intestinal perforation (1), gastrointestinal (GI) haemorrhage (1), GI ulcer haemorrhage (1)	Thyroiditis (3), hyperthyroidism (2), hypothyroidism (3), hypopituitarism (2), adrenal insufficiency (3), diabetic ketoacidosis (DKA) (3), diabetes mellitus (2)
Nivolumab (Opdivo®)	Pneumonitis (4), pneumonia (3), pleural effusion (2)	SJS (10), TEN (1)	-	Hypocortisolism (1), thyrotoxicosis (1), hypophysitis (1), DKA (1)
Dostarlimab (Jemperli)	-	-	-	Hypothyroidism (1)
Atezolizumab (Tecentriq®)	Pneumonitis (2), pneumonia (8)	-	Colitis (1), enterocolitis (1), duodenitis (1), gastroenteritis (1), GI haemorrhage (1)	Thyroiditis (2), hypophysitis (1)
Durvalumab (Imfinzi®)	Pneumonitis (20), pneumonia (4)	-	Colitis (2), cytomegaly colitis (1), duodenitis (1), appendicitis (1)	Thyroiditis (1), hypocortisolism (2), DKA (1)

Serious AEs reported with PD-1 and PD-L1 immune checkpoint inhibitors

(i) Cutaneous toxicities: Stevens-Johnson syndrome, Toxic epidermal necrolysis

Cutaneous immune-related AEs are the most common toxicity associated with ICIs. These AEs can occur in about 70% of patients treated with PD-1 and PD-L1 inhibitors.[4] Most cutaneous AEs are low grade in severity (mild and localised) and usually develop early, at around 4-5 weeks of drug exposure. Rare and serious AEs, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can develop as early as seven days or as late as 140 days after drug initiation.[1,5,6]

As at 30 September 2024, HSA received 58 serious cutaneous AE reports associated with PD-1 and PD-L1 inhibitors. Majority of the reports (44.8%, n=26) were SJS/TEN suspected with PD-1 inhibitors, while the remaining 32 reports described a range of AEs including severe maculopapular rash, palmar-plantar erythrodysaesthesia, dermatitis, bullous eruption, lichen planus, and drug rash with eosinophilia and systemic symptoms (DRESS). Of the 26 SJS/TEN cases, 15 cases were associated with pembrolizumab and 11 were with nivolumab. None were reported with PD-L1 inhibitors. The latency ranged from 6 - 264 days (median : 77 days). About 76.9% (n=20) of the patients had recovered or had uncertain outcomes at the time of reporting.

SJS and TEN are serious and life-threatening AEs, and management of these conditions entails temporary or permanent discontinuation of the culprit drugs.[5,6] It is important for healthcare professionals to monitor patients for cutaneous reactions and identify and withdraw the offending drug when SJS/TEN is suspected. It is also important to counsel patients on early signs, such as rashes and flu-like symptoms so that they can seek early medical attention.

(ii) Pneumonitis

Pneumonitis is a relatively rare but potentially life-threatening immune-related AE.[1,5] Based on a meta-analysis of 20 studies with PD-1 inhibitor-related pneumonitis in patients with advanced cancer, the overall incidence of pneumonitis was 2.7% for monotherapy.[7] The onset and progression of pneumonitis is often insidious and symptoms can be non-specific (dyspnoea, cough, fatigue, chest pain), with latency ranging from 2 months to years following drug exposure.[8] The severity of symptoms ranges from mild to severe and can be fatal in over 10% of cases.[9]

HSA received 35 reports of pneumonitis associated with PD-1 and PD-L1 inhibitors. Twenty-seven reports (77%) involved patients who were treated for lung cancer (NSCLC, SCLC, lung adenocarcinoma) which potentially reflects the usage pattern of these drugs. It could also be a confounder by indication, resulting in a high incidence of respiratory-related AEs in patients. The median time-to-onset was 40 days (range: 0 - 198 days). Majority of the cases (48.6%, n=17) reported severe or life-threatening pneumonitis (CTCAE Grade 3 or 4), while 17.1% (n=6) were mild to moderate cases (CTCAE Grade 1 or 2). The remaining 13.3% (n=12) of the cases did not report AE severity. In a study

involving 315 patients with lung cancer treated with nivolumab or pembrolizumab, most of the patients depicted a high severity of the disease with an earlier onset of within the first two months of treatment initiation.[10] Hence, paying closer attention to this potential serious AE at the start of treatment is recommended as early detection and witholding of the drug may resolve the AE.[10]

While early detection is ideal, ICI-induced pneumonitis remains a diagnosis of exclusion. Causality assessments can be challenging in cancer patients due to a variety of possible alternative causes, including radiation exposure from concurrent radiotherapy, underlying lung disease or cancer and opportunistic pathogenic agents.[1,11] Performing a computed tomography (CT) scan or chest imaging may help differentiate diagnoses of possible tumour progression, pulmonary infections, or pulmonary embolism.

(iii) Gastrointestinal toxicities: Colitis

Gastrointestinal (GI) toxicities, including colitis, are reported with PD-1 and PD-L1 checkpoint inhibitors. According to meta-analysis and systematic review studies, all-grade incidence of colitis was 0.7% to 2% for PD-1 / PD-L1 inhibitors.[12,13] The onset of GI symptoms occurs most often within 5-10 weeks upon initiation of ICIs, but they can also occur or recur months after therapy is discontinued. Patients with colitis often present insidiously with diarrhoea and watery stools. If the condition is not promptly managed, it may develop into serious complications such as toxic megacolon or colonic perforation, which can be fatal. Hence, continuous monitoring of the patient even after stopping therapy is important as immunotherapy may have long-term effects on the immune system.

HSA received 36 GI-related AE reports with PD-1 and PD-L1 inhibitors. The AEs range from non-serious symptoms (e.g., vomiting, diarrhoea, abdominal pain, constipation) to serious conditions such as colitis and enterocolitis (see Table 2 for other serious AEs). There were six reports of colitis, of which five were graded as severe or life-threatening (CTCAE grade 3 - 4). These included severe colitis, cytomegalovirus colitis, enterocolitis, colitis with perforation and colitis with fatality where the patient died of pneumonia. The last case of colitis was ungraded. The median time-to-onset for the AE was 133 days (range: 6 - 246 days). In literature, the median time-to-onset for colitis is also known to be variable and unpredictable, ranging from 1 week - 2 years.[12]

Diagnosis of immune-related colitis remains a diagnosis of exclusion of other causes e.g., infection, irritable bowel disorder or tumour metastasis. As early signs of colitis often present with non-specific symptoms such as diarrhoea and watery stools, confirmation of diagnosis would require blood and stool laboratory tests, endoscopic evaluation and CT imaging for patients with suspected complications.[12,14]

(iv) Endocrinopathies: Thyroiditis, hypothyroidism and hyperthyroidism

Thyroid dysfunction (e.g., thyroiditis, hypothyroidism, hyperthyroidism) is rarely reported with PD-1 and PD-L1 inhibitor therapy. In a study using data from US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) from 2011 to 2020, the incidence of thyroid dysfunction was 2.6%.[15] Hypothyroidism is most frequently reported with an estimated incidence of 3.9 to 8.5%.[16] The time-to-onset of thyroid dysfunction varies greatly, usually occurring within the first 15 weeks of therapy.[17] However, some may occur as early as 7 days or as late as 3 years.[18] Some affect the thyroid glands temporarily and are self-limiting (e.g., thyroiditis), while others have a more permanent effect e.g., hyperthyroidism or hypothyroidism which may require long-term thyroid hormone replacement.[17,18]

HSA received 12 reports of immune-related thyroid AEs associated with PD-1 and PD-L1 inhibitors, describing thyroiditis, hypothyroidism, hyperthyroidism, thyrotoxicosis, elevated T4 hormone level and decreased thyroid stimulating hormone (TSH) level. Majority of the cases (58.3%, n=7) were reported with moderate severity (CTCAE grade 2), while the remaining ones (41.7%, n=5) were severe (CTCAE Grade 3 and 4). The median time-to-onset of the AEs was 70 days (range: 2-183 days).

Although majority of thyroid dysfunctions are mild, the American Society of Clinical Oncology (ASCO) guidelines[5] recommend a low threshold on laboratory derangement suggesting thyroid dysfunction for patients to be referred to an endocrinologist. This allows for closer monitoring so that further tests can be done to detect potential adrenal insufficiency and to manage any further disease progression. Healthcare professionals are advised to be vigilant for thyroid dysfunction AEs as serious ones rarely resolve and may require permanent hormone replacement therapy.[5,19]

Conclusion

Healthcare professionals are advised to look out for serious AEs suspected with the PD-1 and PD-L1 inhibitors and report them to the Vigilance and Compliance Branch of HSA. Please indicate the CTCAE grading* when describing the severity of the AE. The information will be useful for HSA to identify and assess potential safety signals with this class of drugs.

**To indicate the CTCAE grading in the 'Criteria for seriousness – medically significant' field in the manual and online reporting forms on HSA website (https://www.hsa.gov.sg/adverse-events) and in the Critical Medical Information System (CMIS) accessible via the public healthcare institutions' electronic medical records.*

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Answers to AE Case in Focus: Test Yourself

The patient's euglycaemic diabetic ketoacidosis (eDKA) was precipitated by community-acquired pneumonia and predisposed by the sodium-glucose cotransporter 2 (SGLT2) inhibitor, empagliflozin, which she continued taking despite her acute illness of pneumonia and poor oral intake.

Introduction

The rise of SGLT2 inhibitors in diabetes management has been one of the most significant developments in the field of Diabetology over the past decade. This class of drugs work by inhibiting SGLT2 in the kidneys. In healthy individuals, about 90% of glucose is reabsorbed via SGLT2, and the remaining 10% is reabsorbed via SGLT1. By inhibiting SGLT2, these drugs induce glycosuria, which lead to a reduction in blood glucose levels and improved glycaemic control. SGLT2 inhibitors also induce a modest weight loss via caloric loss from the glycosuria. In addition, SGLT2 inhibitors offer substantial cardiovascular and renal protection. Several landmark clinical trials have demonstrated their efficacy in reducing major adverse cardiovascular events,[1,2,3] hospitalisation for heart failure[4,5,6] and progression of chronic kidney disease[7,8,9] in patients with or without type 2 diabetes mellitus. This has led to expanded indications for SGLT2 inhibitors beyond diabetes management, to include patients with heart failure or chronic kidney disease without diabetes. In Singapore, the registered SGLT2 inhibitors include canagliflozin, dapagliflozin and empagliflozin.

Risk of euglycaemic DKA with the use of SGLT2 inhibitors

DKA is recognised as one of the most serious and life-threatening complications of diabetes. It is characterised by a triad of hyperglycaemia, metabolic acidosis and ketosis. In the 2024 American Diabetes Association Consensus Report,[10] the hyperglycaemia criterion for DKA was revised from a glucose level of ≥13.9 mmol/L, to either a glucose level of ≥11.1 mmol/L or a prior history of diabetes (irrespective of the current presenting glucose value). This was done in recognition of the wider range of glucose levels at presentation of DKA.[10] In recent years, the use of SGLT2 inhibitors has also accounted for the majority of cases of eDKA.[10] eDKA often poses as a diagnostic dilemma due to the paradoxical presence of normal or mildly elevated blood glucose levels (i.e., <11.1 mmol/L), as opposed to the traditional understanding of DKA, which is typically characterised by hyperglycaemia. This highlights the importance of considering the patient's clinical presentation, ketone levels and acid-base status and not just blood glucose levels, when evaluating patients for potential DKA. Some of the common presenting symptoms of eDKA are similar to that of DKA, and these include nausea, vomiting, abdominal pain, anorexia and shortness of breath.

Table 1. Diagnostic criteria for DKA and eDKA

	DKA	eDKA
Glucose	≥11.1 mmol/L, or a prior history of diabetes	<11.1 mmol/L
Ketosis	Beta-hydroxybutyrate levels ≥3 mmol/L, or urinary ketones 2+ or greater	Beta-hydroxybutyrate levels ≥3 mmol/L, or urinary ketones 2+ or greater
Metabolic acidosis	pH <7.3 and/or serum bicarbonate <18 mmol/L	pH <7.3 and/or serum bicarbonate <18 mmol/L

As the use of SGLT2 inhibitors continues to rise, there is growing evidence that SGLT2 inhibitors are associated with an increased risk of DKA.[11] *Blau et al*. estimated that SGLT2 inhibitors increase the risk of DKA in patients with type 2 diabetes by seven-fold.[11] Despite that, the overall incidence of eDKA associated with SGLT2 inhibitor use remains low at 0.1% to 0.6%.[12] Common precipitating factors of eDKA include infections, surgery, acute coronary syndromes or stroke, prolonged fasting and trauma.[13] Risk of eDKA is also higher in patients with type 1 diabetes (currently not an approved indication for SGLT2 inhibitor use) and patients who are insulinopaenic (e.g., those with long-standing type 2 diabetes with beta-cell failure, or who have Latent Autoimmune Diabetes in Adults (LADA)).

eDKA arises from a relative or absolute insulin deficiency, combined with elevated counter-regulatory hormones such as catecholamines, glucagon, and cortisol. This hormonal imbalance reduces peripheral glucose utilisation, leading to hyperglycaemia, while simultaneously promoting lipolysis, fatty acid oxidation, and ketone body production. SGLT2 inhibitors contribute to this process by directly stimulating pancreatic alpha-cells and increasing glucagon secretion. Additionally, these inhibitors enhance urinary glucose excretion, reducing the rise in serum glucose levels which explains the euglycaemic condition. Glycosuria also leads to osmotic diuresis and significant volume depletion. If not promptly recognised and treated, eDKA can become life-threatening. Similar to DKA, the mainstays of treatment for eDKA include fluid resuscitation, insulin therapy, electrolyte replacement and treatment of underlying precipitating events.

Local situation

From 2014 to September 2024, HSA received 197 reports of DKA associated with SGLT2 inhibitors. The trend of reports over the years is illustrated in Figure 1*. Of these, 129 (65.5%) cases were reported or assessed as eDKA (blood glucose levels <11.1 mmol/L) based on the available information. Figure 2 shows the proportion of DKA and eDKA reports received. Majority of the patients who experienced eDKA were females (55.8%, n=72) and between 60 to 79 years old (38.8%, n=55).

The most commonly reported SGLT2 inhibitor was empagliflozin, followed by dapagliflozin and canagliflozin. Where time-to-onset of the adverse event is available, the latency of eDKA ranged from one day to about 4.5 years.

**The number of AE reports received is associated with a variable degree of under-reporting and influenced by many factors.*

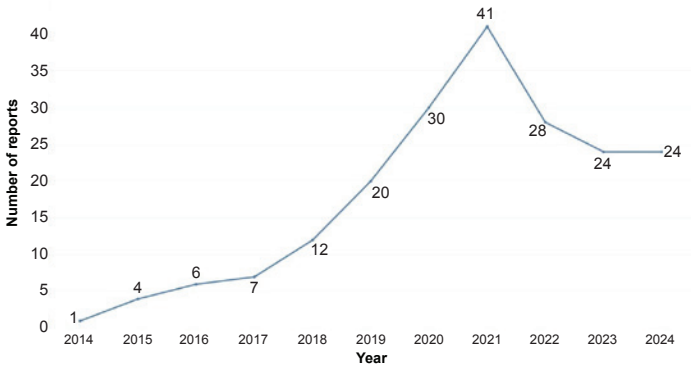

Figure 1. Number of SGLT2 inhibitor-associated DKA reports received by HSA per year from 2014 to September 2024

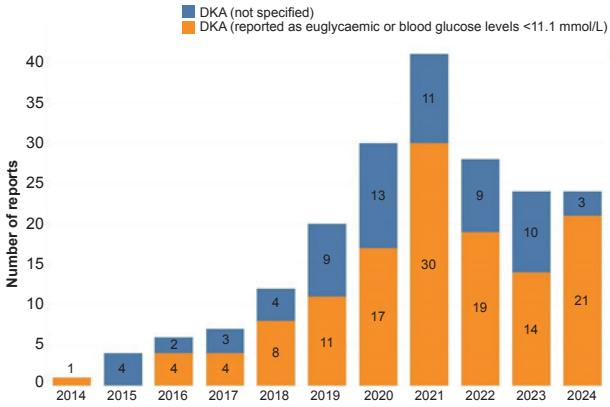

Figure 2. Number of SGLT2 inhibitor-associated eDKA and DKA reports received per year from 2014 to September 2024

Based on a review of 21 patients who were reported to have eDKA in 2024, ten patients had concurrent infections (e.g., upper respiratory tract infection, urinary tract infection, sepsis) occurring with the reported eDKA.

HSA's advisory

Healthcare professionals may wish to consider advising patients to temporarily stop taking SGLT2 inhibitors when precipitants develop, for example, when they are acutely unwell, or 3-5 days prior to surgery. They should avoid insulin omissions or inappropriate insulin dose reductions when acutely unwell.[14] Patients should also be advised to seek medical attention if they develop signs and symptoms of DKA, such as nausea, vomiting, abdominal pain, anorexia and shortness of breath.

Healthcare professionals are encouraged to report serious adverse events, including DKA and eDKA, with the use of SGLT2 inhibitors to the Vigilance and Compliance Branch, HSA.

References

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Biosimilars evaluation: Update on HSA's regulatory considerations for clinical comparability studies

Key Points

- Technological advancements and global accumulated experience with well-characterised biosimilars have reduced the necessity for clinical comparability studies in biosimilar regulatory evaluation.
- HSA has updated its regulatory guidance for biosimilars to reflect the scientific considerations, where clinical comparability data to the innovator biologic products may not be required for certain well-characterised biologics.
- Healthcare professionals are encouraged to report any suspected serious adverse events or efficacy issues associated with biosimilars to HSA.

Biosimilars and its evolving regulations

Biosimilars were introduced in the early 2000s when patent expirations for several biologic products prompted the development of alternative versions. As biologic products were complex and there was limited experience with their development, regulatory requirements for biosimilar approvals were extensive and conservative.

Biosimilars are required to go through a scientifically rigorous development pathway based on a stepwise head-to-head comparability to the reference biologic product (RBP). This stepwise approach progressively builds on the totality of evidence for biosimilarity, with each step informing on how subsequent studies should be designed. The process begins with a comprehensive physicochemical and biological characterisation of the product assessed through analytical methods which is the most critical step in establishing biosimilarity. If this initial characterisation demonstrates high similarity, it may allow for a reduced scope of subsequent steps. The next step involves non-clinical studies evaluating comparative functionality and toxicity. The robustness of data from the analytical and non-clinical studies inform on the design and can potentially reduce the extent of the final step, the clinical comparability based on comparative pharmacokinetics (PK), pharmacodynamics (PD) (where applicable), safety, efficacy, and immunogenicity. This approach ensures a thorough comparison between the biosimilar and the reference biological product at multiple levels. It also demonstrates similarity and that there are no clinically meaningful differences between the RBP and the biosimilar.

Updates on the current regulatory landscape

As regulatory bodies and pharmaceutical companies accumulated experience with biosimilars, we have gained a deeper understanding of the development and assessment process. In addition, analytical and functional characterisation methods underwent significant advancements, becoming more sophisticated and sensitive. State-of-the-art technologies have revolutionised the field, enhancing the ability to analyse and compare complex biological molecules and enabling more precise comparisons between biosimilars and their reference products at both the molecular and functional levels. This has led to well-characterised biologics and biosimilars. Notably, well-designed analytical studies were able to detect product-related differences compared to clinical trials. Furthermore, it became evident that when robust analytical similarity was established, clinical efficacy studies seldom contributed additional critical information to the overall assessment for biosimilarity.[2,3]

These advancements and experience has led to a reconsideration of the role and extent of clinical trials in biosimilar development programs. In 2022, the World Health Organization (WHO) updated its guidelines on the evaluation of biosimilars. The new WHO guidelines indicated that clinical efficacy studies are typically unnecessary if sufficient evidence of biosimilarity is provided through other components, particularly high-quality analytical data and PK/PD studies. This represented a significant shift from the earlier approach that generally required clinical efficacy trials.

HSA's updated regulatory approach

In line with these global developments, HSA has assessed this new approach and updated its regulatory guidance* for biosimilar products. For certain well-characterised biosimilars, clinical comparability data to innovator biologic products would no longer be required. This approach emphasises the in-depth physicochemical and functional characterisation and validated PK/PD endpoints as surrogates for clinical comparability.

Healthcare professionals can refer to the FAQs[1] on HSA's website for the scientific rationale behind this approach. This approach balances scientific progress with regulatory rigour to expedite access to cost-effective therapies, while maintaining high standards of efficacy and safety.

To date, HSA has registered 35 biosimilars. Some of these include biosimilars of filgrastim, infliximab, adalimumab, trastuzumab and bevacizumab.[∞]

**Guidance on therapeutic product registration in Singapore, Chapter E, Section 21.4.2*

∞The list of registered biosimilars can be found here: https://www.hsa.gov.sg/e-services/infosearch

Adverse event reporting

As part of continuous monitoring of biosimilars to detect any potential safety concerns related to its use in the market, healthcare professionals are encouraged to be vigilant and report any suspected serious adverse events (AEs) to the Vigilance and Compliance Branch of HSA through the following channels found on our website: https://www.hsa.gov.sg/adverse-events or the Critical Medical Information Store (CMIS) accessible via the public healthcare institutions' electronic medical record system. For efficacy issues, please report via email: HSA_productsafety@hsa.gov.sg to HSA. It is important to provide the **brand name** and **batch/lot number** of the biosimilar to facilitate the detection of brand- or batch-specific AEs and quality issues.

References

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2. *Clin Pharmacol Ther. 2023 Jan;113(1):108-123.*
3. *BioDrugs. 2023 Nov;37(6):855-871.*

Please send your enquiries, comments and suggestions to:

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