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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 1: Test Yourself Pg 5

Case 1

A 70-year-old female presented to the Emergency Department (ED) with a one-day history of non-vertiginous giddiness, altered mental state and confused speech. She was also unable to do simple arithmetic questions. Prior to that, she had visited a General Practitioner (GP) with left cheek and lip lesions and was treated for herpes zoster with etoricoxib, gabapentin and valacyclovir. On examination, she was afebrile and haemodynamically stable. She was orientated to time, place and person with no focal deficits on neurological examination. Investigations showed a normal white blood cell count, C-reactive protein, thyroid function test and serum calcium. The contrasted computed tomographic (CT) scan of her brain was also unremarkable.

Case 2

A 64-year-old female presented to the ED with a two-day history of altered mentation with increasing drowsiness and confusion. She had a rash three days ago and was diagnosed with herpes zoster by her GP. She was treated with topical acyclovir, oral valacyclovir and vitamin B supplement. On admission, she was diagnosed with disseminated zoster infection with possible meningoencephalitis and was treated with ceftriaxone, vancomycin and intravenous acyclovir. On examination, she was alert and was able to obey 1-step commands. Her Glasgow coma scale (GCS) score was 14. There were no focal neurological deficits, and her muscle power assessment score was 5 for all four limbs. On the second day, her neurological state deteriorated and she developed chorea-like movements and subsequently myoclonic jerks. Her GCS score fell to 6. Investigations which included CT and magnetic resonance imaging of the brain was unremarkable.

Q: What is the likely cause of the neurological symptoms in these patients?

AE Case in Focus 2: Test Yourself Pg 5

A 4-year-old boy was rushed to the ED with acute flushing, angioedema, itchy throat and voice hoarseness minutes after taking a sachet of probiotics. He did not consume any other food or medication. His parents immediately administered an adrenaline autoinjector (Epipen) and rushed him to the ED. The patient has an allergy action plan and holds an Epipen because of his food allergies to cow's milk and nuts.

Q: What could have caused this patient's presentation?

Dear Healthcare Professional Letters on safety concerns

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 December 2022.

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TOPICAL CORTICOSTEROIDS AND RISK OF TOPICAL STEROID WITHDRAWAL

Key Points

- A rebound flare of dermatitis, termed Topical Steroid Withdrawal (TSW), has been reported following discontinuation of topical corticosteroids (TCS)
- It is often preceded by a prolonged period of TCS use of escalating potency and frequency
- Signs and symptoms of TSW, which may be extensive and differ from the original dermatosis, include erythema, oedema, scaling, acneiform lesions, burning and itch
- Healthcare professionals are advised to consider the potential of rebound dermatitis and TSW when prescribing longer durations of TCS

Topical corticosteroids (TCS) are used for the relief of the inflammatory and pruritic manifestations of various dermatoses, including eczema and psoriasis. The locally registered TCS include betamethasone, clobetasol, desonide, diflucortolone, fluocinolone, fluticasone, hydrocortisone, mometasone and triamcinolone. Based on HSA's experience, certain illicit skin-lightening creams have been found to contain these steroid as adulterants.

About topical steroid withdrawal (TSW)

Topical steroid withdrawal (TSW) refers to a mixed group of symptoms that has also been referred to as topical steroid addiction, red skin syndrome or steroid dermatitis. It has been suggested that this syndrome arises from a physical dependence on TCS, particularly in the context of increasing potency and frequency, and prolonged use of TCS. A rebound worsening of skin manifestations after discontinuation of TCS may occur, which may be more extensive or with a different morphological appearance from the initial skin condition.[1]

Systematic reviews have attempted to collate and characterise the clinical features of TSW from published case reports, case series and cross-sectional studies.[2,3] TSW was reported as predominantly affecting the face and genital area, with common symptoms including itch, burning and stinging. The duration of TCS use in the majority of the cases was 6 months or longer, and the time-to-onset of TSW ranged from days to months after TCS discontinuation. Two distinct clinical presentations of TSW were observed: 1) an erythematoedematous subtype that occurred in patients with an underlying eczematous dermatosis, presenting more frequently with burning, erythema and oedema, and 2) a papulopustular subtype that occurred primarily in patients who used TCS for cosmetic purposes (e.g., illicit skin-lightening creams). The reviews concluded that TSW is likely a distinct clinical adverse effect resulting from prolonged, inappropriate, and frequent use of moderate- to high-potency TCS. However, the reviewed evidence (i.e., observational studies) was of low quality and at risk of bias, necessitating further well-designed studies to better understand and define this entity.

The recognition and diagnosis of TSW remains a challenge. There is no consensus on the diagnostic criteria for TSW, and its features overlap with other clinical entities, such as allergic contact dermatitis and a flare-up of the pre-existing inflammatory condition or skin infection.[1, 2] In addition, investigations (such as a skin biopsy) are generally of limited use to distinguish TSW from a flare of the pre-existing skin condition. Proposed mechanisms for TSW include rebound vasodilation mediated by elevated nitric oxide (NO), dysregulation of glucocorticoid receptors and tachyphylaxis. However, current evidence is limited and in certain areas, contradictory.

UK Medicines and Healthcare products Regulatory Agency's review

In 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA) conducted a review of evidence based on published literature as well as cases of TSW associated with TCS where the majority of these cases were reported by patients.[4] The agency noted growing evidence of cases of TSW which were associated with long-term continuous or inappropriate use of TCS. Although the UK MHRA was unable to estimate the incidence of TSW, the agency considered reports of severe withdrawal reactions as being very infrequent given the number of patients treated with TCS. The agency's review concluded that TCS remains a safe and effective treatment for skin disorders when used correctly (i.e., lowest potency needed over short periods of time or intermittently over an extended period).

Local situation and HSA's advisory

To date, HSA has received three reports of TSW, all of which were associated with long-term (several years) use of topical products that were tested to be adulterated with potent TCS. In response, HSA had issued a press release to warn members of the public against the purchase of such products from dubious sources and to raise awareness on the prolonged use of TCS and their associated withdrawal reactions.[5] An ADR News bulletin article was also published to inform healthcare professionals of such illegal products purchased by consumers and to be vigilant of potential TSW AEs arising from the use of such products in consumers.[6]

As HSA continues to monitor reports of TSW with the use of TCS, healthcare professionals are advised to take into consideration the above information when prescribing TCS, and to consider the possibility of TSW in patients with a history of continuous prolonged TCS use who present with suggestive clinical signs. Healthcare professionals are also encouraged to report to HSA any suspected cases of TSW related to the use of TCS.

Acknowledgement

HSA would like to thank Dr Ellie Choi and Dr Nisha Suyien Chandran from the Division of Dermatology, Department of Medicine, National University Hospital for their contributions to this article.

References

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UPDATES ON ADULTERATED PRODUCTS REPORTED TO HSA

Key Points

- Weight loss products were the most common category of adulterated products detected by HSA. Sibutramine, a substance banned since 2010 due to an increased risk of heart attacks and strokes, was the most common adulterant in these products
- On 1 August 2022, HSA launched a voluntary notification system for companies to notify their health supplements and traditional medicines with the authority. The aim of this initiative is to establish a local database of safe and good quality health supplements and traditional medicines that consumers can refer to when they make their purchases

Between December 2021 and October 2022, HSA issued five press releases to warn the public of 11 adulterated products. HSA was alerted to these products through adverse event (AE) reports from healthcare professionals and public feedback. HSA's Pharmaceutical Laboratory tested the products and found that they contained potent medicinal ingredients. Most of the adulterated products were marketed for slimming or weight loss (45%). The rest were marketed for general health, joint pain, skin conditions (including psoriasis and eczema) or sexual enhancement. Similar to our previous update on adulterated products published in the December 2021 issue, the most common adulterant found in slimming products was sibutramine, a prescription-only weight loss medicine which has been banned since 2010 in Singapore due to an increased risk of heart attacks and strokes. All but one of the adulterated products were marketed on local e-commerce and social media platforms. HSA has worked with the platform administrators to remove the affected listings and issued warnings to the sellers. The relevant press releases can be found on HSA's website: https://www.hsa.gov.sg/announcements/press-release. Summaries of the press releases are provided below.

On 1 August 2022, HSA launched a voluntary notification system for companies to notify their health supplements and traditional medicines with the authority. The aim of this initiative is to establish a local database of safe and good quality health supplements and traditional medicines that consumers can refer to when they make their purchases. The notification process is conducted in phases, with the first phase for vitamin and mineral supplements as well as products for weight loss, pain relief and male vitality enhancement. HSA will include other product types in subsequent phases. In order to be included in the database of notified products (https://www.hsa.gov.sg/vns-list), companies are required to demonstrate that products meet the necessary safety and quality standards substantiated by the relevant documents. Products intended for weight loss, pain relief and male vitality enhancement have to be screened for adulterants.

'X-Gout', 'dcr Natural Herbs Honey Enzyme', 'KMS2 Dark Chocolate Mocha Botanical Beverage', 'Speedy Slim Capsules (Black)', 'Speedy Slim Capsules (Gold)'

Press release issued on 30 December 2021

Five products marketed on local e-commerce and social media platforms were found to be adulterated following reports of serious AEs and feedback from members of the public. A woman in her 40s developed Cushing's syndrome after taking 'X-Gout' for a year to alleviate her knee pain. She presented with rapid weight gain, shortness of breath, swelling of the lower limb and was subsequently diagnosed with diabetes. The product was tested to contain four medicinal ingredients (dexamethasone, indomethacin, piroxicam and paracetamol) which could lead to adverse health effects with inappropriate use. For instance, long-term unsupervised use of steroids such as dexamethasone can cause diabetes, Cushing's syndrome, osteoporosis and mood changes. Another case of Cushing's syndrome was reported in a man in his 40s after he took 'dcr Natural Herbs Honey Enzyme' for about six months. He experienced withdrawal symptoms such as loss of appetite, lethargy and rashes upon stopping the product. Although samples of this product were found to contain only paracetamol, it could not be ruled out that other batches might contain other adulterants including steroids.

'KMS2 Dark Chocolate Mocha Botanical Beverage' was found to contain sulphamethoxydiazine and amethocaine after a consumer reported that he experienced fast heartbeat, thirst and dry mouth after consuming the product for a few days. The sellers claimed that the product "speeds up fat burning by inducing heat, helps soothe digestive systems and boost metabolic cycles to reduce appetite and is safe without rebounding weight". Two other weight loss products, 'Speedy Slim Capsules (Black)' and 'Speedy Slim Capsules (Gold)', also had exaggerated claims such as "target at breaking down stubborn extra fat", "cut off starch absorption", and "losing weight and clearing fat". High levels of sibutramine were detected in these products after members of the public alerted HSA to their sales on Instagram.

Figure 1. 'X-Gout', 'dcr Natural Herbs Honey Enzyme', 'Speedy Slim Capsules' (Gold)

'Traditional Herbs Preparation XPE' and 'FS++ Slimming Supplements by JPJ Slim'

Press release issued on 1 March 2022

A woman in her 60s, who obtained 'Traditional Herbs Preparation XPE' from Malaysia through a friend, took it for over nine months to alleviate her joint pain. The product was labelled to contain natural herbs and was marketed for general health. Although the consumer experienced quick relief of her joint pain, it worsened when she reduced the dose or stopped taking it. HSA tested the product and detected six medicinal ingredients: dexamethasone, chlorpheniramine, ibuprofen, lovastatin, chloramphenicol and tetracycline.

Separately, HSA received a report from a consumer who experienced insomnia, headache and confusion after taking 'FS++ Slimming Supplements by JPJ Slim'. The product was purchased via a social media platform that carried testimonials on its quick slimming results. The product was tested to contain sibutramine, which could have led to serious health consequences such as coronary artery disease, arrhythmia, stroke and psychosis with continued intake.

'AK-II Phenomenal King' and 'Premium Pro S Flash'

Press release issued on 27 April 2022

HSA was alerted to the online sale of 'AK-II Phenomenal King' by a member of the public. The product was marketed as a natural product for sexual enhancement and claimed to be "devoid of animal element, devoid of stimulants, devoid of side effects". HSA found that the product contained up to over 60 times the usual dose of tadalafil, a medicinal ingredient used to treat erectile dysfunction. Inappropriate use of tadalafil can increase the risk of serious AEs, including heart attacks, stroke, palpitations, visual disturbances and priapism. It can also cause severe hypotension in those who are on concurrent antihypertensives, alpha-adrenergic antagonists (e.g., prazosin and terazosin) and is contraindicated with concurrent use of nitrates due to its vasodilatory effects.

'Premium Pro S Flash' was tested to contain high levels of sibutramine after HSA received feedback from a consumer who experienced fast heart rate, insomnia and nausea after taking it. 'Premium Pro S Flash' was advertised online as a weight loss product containing natural ingredients such as red ginseng, red sage and wild yam. It was also promoted as a new version of 'Flash Slim', another product adulterated with sibutramine which HSA alerted the public to in March 2021.[2] The lack of proper instructions on how to take the product, the absence of manufacturing information, and the misleading marketing claims were tell-tale signs that this product was not from a reliable source.

Figure 2. 'AK-II Phenomenal King' and 'Premium Pro S Flash'

'Prime Kopi Pejuang 3 In 1'

Press release issued on 26 May 2022

'Prime Kopi Pejuang 3 in 1' was marketed online as a natural product containing "herbal ingredients of high quality" that enhances men's sexual health. After receiving two AE reports from consumers, HSA tested the coffee product and detected a high concentration of tadalafil. Consumers who take the product according to the labelled instructions of one sachet daily would be overdosing on more than 10 times the usual prescribed dose of tadalafil. One consumer presented to the hospital emergency department with body aches, chills, migraine and tightness around the jawline. Another consumer experienced priapism of about 4 hours after taking the product. Priapism can lead to penile tissue damage and permanent loss of potency if not treated immediately.

'Star Cream (星星膏)'

Press release issued on 9 June 2022

A doctor alerted HSA to 'Star Cream' as he suspected that the product was adulterated. A four-month-old infant, who had 'Star Cream' applied on him for diaper rash since he was two weeks old, presented to the hospital with persistent vomiting, convergent squint and a bulging fontanelle, consistent with signs of intracranial hypertension. Further investigations confirmed that he had Cushing's syndrome due to steroid toxicity. The infant's parents had bought 'Star Cream' online following the recommendation of their confinement nanny. The product was marketed as a homemade cream containing natural herbal extracts, with antibacterial and antifungal properties and claimed to have "no steroids". It was advertised to be "suitable for all skin types", including skin conditions such as acne, eczema, mosquito bite, psoriasis and skin ringworms. There were also multiple consumer reviews on the e-commerce and social media platforms regarding its quick relief of various chronic skin conditions. HSA detected clobetasol propionate and ketoconazole in the cream. These ingredients can pose serious health risks, especially in infants and children, if used without medical supervision.

Figure 3. 'Star Cream'

Conclusion

Products adulterated with potent medicinal ingredients are harmful and can cause serious AEs in consumers. Healthcare professionals can facilitate the detection of adulterated products by carefully taking the patient's medical history, including their complementary health products and supplements intake. Healthcare professionals may also wish to advise patients to refer to the database of notified health supplements and traditional medicines before making their purchases.

AE CASE IN FOCUS 1: TEST YOURSELF

Case 1

A 70-year-old female presented to the emergency department (ED) with a one-day history of non-vertiginous giddiness, altered mental state and confused speech. She was also unable to do simple arithmetic questions.

One day prior to ED presentation, she had presented to a General Practitioner (GP) with left cheek and lip lesions and was treated for herpes zoster with etoricoxib, gabapentin and valacyclovir. Her past medical history included diabetes mellitus, end-stage kidney disease (on haemodialysis) and ischaemic heart disease.

On examination, she was afebrile and haemodynamically stable. She was orientated to time, place and person with no focal deficits on neurological examination. A vesicular rash over her left face and upper lip was observed. Investigations on admission showed a normal white blood cell count, C-reactive protein, thyroid function test and serum calcium. A contrasted computed tomographic (CT) scan of her brain was unremarkable.

Case 2

A 64-year-old female presented to the ED with a two-day history of altered mentation with increasing drowsiness and confusion.

She was noted to have developed a rash three days prior to admission and was diagnosed with herpes zoster by her GP and was treated with topical acyclovir, oral valacyclovir and vitamin B supplement. The initial clinical impression on admission was disseminated zoster infection with possible meningoencephalitis and the patient was commenced on ceftriaxone, vancomycin and intravenous acyclovir. Her medical history included end-stage kidney disease (on peritoneal dialysis), diabetes mellitus and systemic lupus erythematosus.

On examination, she was alert and was able to obey 1-step commands. Her Glasgow coma scale (GCS) score was 14. There were no focal neurological deficits and her muscle power assessment score was 5 for all 4 limbs. A vesicular rash over the right axillary region was noted.

On the second day of admission, her neurological state deteriorated with the development of chorea-like movements and subsequently myoclonic jerks and drop in GCS to 6 (E1V1M4). Physical examination revealed normal tone and reflexes in her limbs, with bilateral reactive pupils.

Investigations including CT and magnetic resonance imaging of the brain did not reveal any cause for her neurological deterioration. A lumbar puncture showed cerebrospinal fluid (CSF) nucleated cells of 1 cell/uL, protein of 0.66g/L and glucose of 3.4mmol/L (all results within normal range), with negative microbiology and cytology.

Question: What is the likely cause of the neurological symptoms in these patients?

HSA would like to thank Adjunct Assistant Professor Yeo See Cheng, Head & Senior Consultant, Department of Renal Medicine and Dr. Benjamin Khoo Zhi En, Consultant, Department of Renal Medicine at Tan Tock Seng Hospital for contributing this article.

Answers can be found on page 7

AE CASE IN FOCUS 2: TEST YOURSELF

A 4-year-old boy was rushed to the ED with acute flushing, angioedema, itchy throat and voice hoarseness minutes after taking a sachet of probiotics. He did not consume any other food or medication. His parents immediately administered an adrenaline autoinjector (Epipen) and rushed him to the ED. He responded to treatment and was discharged well.

The patient has an allergy action plan and holds an Epipen because of his food allergies to cow's milk and nuts. Two months prior to this visit, he visited the ED for food-anaphylaxis after the consumption of milk.

Question: What could have caused this patient's presentation?

HSA would like to thank Dr. Goh Si Hui, Consultant, Allergy Service, Department of Paediatrics, KK Women's and Children's Hospital for contributing this article.

Answers can be found on page 8

JANUS KINASE (JAK) INHIBITORS AND RISK OF MAJOR ADVERSE CARDIOVASCULAR EVENTS, MALIGNANCY, THROMBOSIS AND DEATH

Key Points

- A post-authorisation safety study (ORAL Surveillance) found an increased risk of major adverse cardiovascular events (MACE), malignancy, thrombosis and death with tofacitinib, a Janus Kinase (JAK) inhibitor, compared to tumour necrosis factor (TNF) inhibitors in patients with rheumatoid arthritis who were 50 years of age or older, and with at least one additional cardiovascular risk factor
- Other JAK inhibitors used in the treatment of inflammatory conditions may have similar risks as observed with tofacitinib in the ORAL Surveillance study
- HSA conducted a benefit-risk assessment and concluded that the benefit-risk profile of JAK inhibitors for the treatment of inflammatory conditions remains positive for their approved indications in Singapore
- Healthcare professionals are advised to consider the benefits and risks of JAK inhibitors before prescribing them, and to monitor their patients for these potential risks during treatment, particularly the elderly, current or past smokers, or those with other cardiovascular, malignancy or thromboembolic risk factors

HSA has completed its assessment on the risk of major adverse cardiovascular events (MACE), malignancy, thrombosis and death associated with Janus Kinase (JAK) inhibitors for the treatment of inflammatory conditions. The assessment was conducted in response to findings from a post-authorisation safety study (ORAL Surveillance), which found an increased risk of these adverse events (AEs) with tofacitinib compared to tumour necrosis factor (TNF) inhibitors in rheumatoid arthritis (RA) patients who were 50 years of age or older, and with at least one additional cardiovascular risk factor.

Based on currently available information, HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), has concluded that the benefit-risk profile of JAK inhibitors for the treatment of inflammatory conditions remains positive for their approved indications, where the use of JAK inhibitors is already limited to second line or later therapy in Singapore. As other JAK inhibitors used in the treatment of inflammatory conditions may have similar risks as observed with tofacitinib in the ORAL Surveillance study, healthcare professionals are advised to consider the benefits and risks of JAK inhibitors before prescribing these drugs, and to monitor their patients for these potential risks during treatment, particularly the elderly, current or past smokers, or with other cardiovascular, malignancy or thromboembolic risk factors.

Locally approved JAK inhibitors

JAK inhibitors are immune modulating drugs used for the treatment of inflammatory conditions such as RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis. The JAK inhibitors approved in Singapore for the treatment of inflammatory conditions are Xeljanz®, Pfizer Private Limited (tofacitinib), Olumiant®, DKSH Singapore Pte. Ltd. (baricitinib), Rinvoq®, AbbVie Pte. Ltd. (upadacitinib) and Cibinqo®, Pfizer Private Limited (abrocitinib). Other JAK inhibitors that are not indicated for the treatment of inflammatory conditions (e.g., ruxolitinib) were not included in the scope of HSA's benefit-risk assessment.

Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study[1]

The ORAL Surveillance study was a randomised, open-label, noninferiority trial evaluating the safety of tofacitinib at two doses (5mg and 10mg twice daily) compared with a TNF inhibitor[a] in patients with active RA despite treatment with methotrexate (MTX). The population enrolled were at least 50 years of age and had at least one additional cardiovascular risk factor.[b] The co-primary endpoints of the study were adjudicated MACE[c] and malignancy (excluding nonmelanoma skin cancer [NMSC]). The noninferiority of tofacitinib would be shown if the upper limit of the two-sided 95% confidence interval for the hazard ratio was less than 1.8 for the combined tofacitinib doses as compared with a TNF inhibitor.

A total of 4,362 subjects were randomised to receive treatment with at least one dose of tofacitinib 5mg twice daily (n=1,455), tofacitinib 10mg twice daily (n=1,456), or a TNF inhibitor (n=1,451). The demographic and clinical characteristics of patients at baseline were generally similar across trial groups. Most of the patients were female (78%) and Caucasian (76.9%), with a mean age of 61 years (median: 60 years; range: 50 to 88 years). In February 2019, patients who were treated with tofacitinib 10mg twice daily were transitioned to the lower dose of 5mg twice daily, after an interim analysis of the ongoing study noted a higher incidence of pulmonary embolism and mortality among patients receiving tofacitinib 10mg twice daily than among those receiving tofacitinib 5mg twice daily or a TNF inhibitor. The median on-study follow-up time was four years and patients were analysed in their originally assigned group, including those who were switched from tofacitinib 10mg to 5mg twice daily.

In the final analysis, noninferiority was not shown for the combined doses of tofacitinib as compared with a TNF inhibitor for the co-primary endpoints of MACE and malignancy (excluding NMSC) (Table 1). The incidences of MACE and malignancy were higher with the combined tofacitinib doses than with a TNF inhibitor (Hazard ratio 1.33 [95% CI 0.91 – 1.94] and 1.47 [95% CI 1.04 – 2.09], respectively). The signal of malignancy was mainly driven by higher incidences of lung cancer and lymphoma. Adjudicated venous thromboembolism (VTE) and death from any cause were more frequent with both tofacitinib doses than with a TNF inhibitor. A dose-dependent increased risk for MACE, VTE and death was observed for both tofacitinib doses compared with the TNF inhibitor. In subgroup analyses stratified by age, the incidence rates of MACE and malignancy across trial groups were higher in patients 65 years of age or older than those younger than 65 years of age. Among patients aged 65 years and older, both tofacitinib doses were associated with a higher risk of MACE and malignancy than with a TNF inhibitor.

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[a]In the US, Puerto Rico and Canada, subjects randomised to receive a TNF inhibitor received adalimumab 40mg every two weeks by subcutaneous (SC) injection. In all other countries, subjects randomised to receive a TNF inhibitor received etanercept 50mg once weekly by SC injection.

[b]Current cigarette smoker, hypertension, high density lipoprotein (HDL) < 40mg/dL, diabetes mellitus, family history of premature coronary heart disease, extra-articular rheumatoid arthritis, history of coronary artery disease.

[c]MACE was defined as cardiovascular death (sudden cardiac death and death due to acute myocardial infarction, heart failure, stroke, cardiovascular procedures, cardiovascular haemorrhage, and other cardiovascular causes [e.g., peripheral artery disease], but not death due to pulmonary embolism), nonfatal myocardial infarction, and nonfatal stroke, including reversible focal neurologic defects with image evidence of a new cerebral lesion consistent with ischaemia or haemorrhage.

Table 1. Incidence of adverse events and hazard ratios

Event Incidence, % (Hazard ratio, 95% CI)	Tofacitinib 5mg BD	Tofacitinib 10mg BD	Tofacitinib combined doses	TNF inhibitor (Reference)
MACE	3.2% (1.24, 0.80 – 1.90)	3.5% (1.43, 0.94 – 2.18)	3.4% (1.33, 0.91 – 1.94)	2.5%
Malignancy (excl. NMSC)	4.3% (1.47, 0.99 – 2.18)	4.1% (1.48, 0.99 – 2.19)	4.2% (1.47, 1.04 – 2.09)	2.9%
VTE	1.2% (1.66, 0.76 – 3.63)	2.3% (3.52, 1.74 – 7.12)	NA	0.7%
Death from any cause	1.8% (1.49, 0.81 – 2.74)	2.7% (2.37, 1.34 – 4.18)	NA	1.2%

NA: Not available

International regulatory actions

International regulatory health authorities, namely the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Health Canada have conducted safety reviews in light of the increased risks observed with tofacitinib in the ORAL Surveillance study. In addition to tofacitinib, their safety reviews were also extended to other JAK inhibitors used in the treatment of inflammatory conditions.[2-7]

(a) Xeljanz® (Tofacitinib)

The reviews by these regulatory agencies concluded there was an increased risk of MACE, malignancy and thrombosis with tofacitinib compared to TNF inhibitors. As a result, all three agencies recommended for the tofacitinib package inserts (PI) to be updated with warnings on the increased risks observed in the ORAL Surveillance study. In addition, the US FDA and Health Canada also recommended changes to the approved indications of tofacitinib. The US FDA limited all approved uses of tofacitinib to patients who have had an inadequate response or intolerance to one or more TNF inhibitors, while Health Canada limited the use of tofacitinib for RA to patients who have had an inadequate response or intolerance to MTX and at least one other disease modifying anti-rheumatic drug (DMARD).

(b) Other JAK inhibitors for inflammatory conditions

The US FDA, EMA and Health Canada concluded that other JAK inhibitors used in the treatment of inflammatory conditions (e.g., baricitinib and upadacitinib) may have similar risks as seen with tofacitinib in the ORAL Surveillance study. The US FDA extended its warnings and limitation on use for tofacitinib to other JAK inhibitors used for the treatment of inflammatory conditions, whereas Health Canada and EMA only recommended for updated warnings on the risks observed with tofacitinib in the ORAL Surveillance study, with no changes to the approved indications.

Local adverse event reports of MACE, malignancy, thrombosis or death associated with JAK inhibitors

To-date, HSA has received two AE reports of breast cancer and death associated with the use of tofacitinib. The event of breast cancer was assessed by the reporting company to be an intercurrent medical condition unrelated to tofacitinib treatment, while confounding factors (e.g., concomitant use of other chemotherapeutic agents) were present for the case with a fatal outcome following infections. HSA has also received one AE report of stroke associated with upadacitinib use. However, the event of stroke was assessed to be unlikely related to upadacitinib treatment and the patient was subsequently restarted on the same JAK inhibitor for treatment of RA with no reported issues. There have been no local AE reports of MACE, malignancy, thrombosis, or death with baricitinib and abrocitinib.

HSA's benefit-risk assessment

HSA's benefit-risk assessment took into consideration the findings from the ORAL Surveillance study, information provided by the pharmaceutical companies, local usage of JAK inhibitors, expert opinions of local clinicians (i.e., rheumatologists, gastroenterologists, dermatologists) and regulatory actions taken by the international health regulatory authorities. Based on currently available information, HSA, in consultation with its PVAC, has assessed that the benefit-risk profile of JAK inhibitors remains positive for their approved indications in Singapore, where the use of JAK inhibitors is already limited to second line or later therapy. As the mechanism of occurrence of these AEs remains unknown, the risk of these AEs with other JAK inhibitors cannot be excluded, as they share a similar mechanism of action.

HSA's advisory and actions

Healthcare professionals are advised to consider the benefits and risks of JAK inhibitors before prescribing these drugs, and to monitor their patients for these potential risks during treatment, particularly the elderly, current or past smokers, or with other cardiovascular, thromboembolic or malignancy risk factors.

HSA has issued a Dear Healthcare Professional Letter on 17 November 2022 to inform healthcare professionals of HSA's advisory and actions following our benefit-risk assessment of JAK inhibitors.[8] HSA is working with the product registrants to strengthen the PIs of JAK inhibitors approved for the treatment of inflammatory conditions to include warnings on the increased risks of MACE, malignancy, thrombosis and death observed with tofacitinib in the ORAL Surveillance study. HSA will continue to closely monitor the international and local developments of this issue and update healthcare professionals of any new significant findings.

Healthcare professionals are encouraged to report any suspected serious AEs related to use of JAK inhibitors to the Vigilance and Compliance Branch of HSA.

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ANSWER TO AE CASE IN FOCUS 1: TEST YOURSELF

The neurological symptoms experienced by both patients are likely attributed to the use of acyclovir and valacyclovir.

Corroborative history revealed that the patient in Case 1 was prescribed valacyclovir 1g TDS and she had consumed a total of 3 doses prior to her presentation at the emergency department (ED). Following her admission, the patient's mentation improved after haemodialysis, with concurrent renal-dose adjustment of acyclovir. Her facial lesions improved and she made an uneventful recovery.

In Case 2, the patient was prescribed valacyclovir 1g TDS and two doses were ingested. Upon admission, two further doses of intravenous acyclovir 500mg Q8H were administered, which likely accounted for the progressive neurological decline. Peritoneal dialysis was continued but patient's mentation remained poor hence a decision was made for a temporary haemodialysis treatment with improvement in neurological status. The patient subsequently made an uneventful recovery.

Neurotoxicity associated with acyclovir and valacyclovir

Acyclovir and valacyclovir are commonly used and neurotoxicity may occur in certain susceptible patients.[3,4] Neurotoxicity can manifest as confusion, dizziness, drowsiness, stupor, coma and psychiatric symptoms, among others.[3] Risk factors that have been reported largely in case reports and case series include older age, renal impairment and a high dose of acyclovir.[3] A differential common to these presentation is Varicella Zoster virus meningoencephalitis and a careful history with regards to acyclovir and valacyclovir dosing would help in differentiating this from neurotoxicity, with where the presence of fever, headache, meningeal symptoms (such as a stiff neck and cranial neuropathy) usually suggesting an infection. Furthermore, the presence of pleocytosis and a positive polymerase chain reaction or antibodies to virus in cerebrospinal fluid (CSF) are indicators of infection.

Renal Drug Dosing and Pharmacokinetics of Acyclovir and Valacyclovir

Dose adjustment according to kidney function is recommended for acyclovir and valacyclovir. A commonly recommended dose of valacyclovir for patients with end-stage kidney disease is 500mg Q24H and for intravenous acyclovir 2.5-5mg/kg/dose Q24H. Acyclovir distributes widely in body fluids and is principally excreted by the kidney.[1] Notably, acyclovir has poor oral bioavailability. On the other hand, valacyclovir has a 3 to 5 fold greater oral bioavailability compared to acyclovir and a dose of 250mg 4x/day generates the same area under the curve (AUC) in a plasma drug concentration-time curve as oral acyclovir 800mg 5x/day.[2]

In patients with reported acyclovir and valacyclovir neurotoxicity, the administered dose of acyclovir and valacyclovir was higher than the renal-adjusted recommended dose in 60% of cases in a systematic review.[3] Dose adjustment of acyclovir and valacyclovir for renal impairment and end-stage kidney disease is essential to reduce the likelihood of toxicity, although neurotoxicity (associated with documented elevated of serum acyclovir) can occur even when acyclovir dose is properly adjusted for kidney function.[5] Serum or CSF acyclovir level is not required for diagnosis.[3] Drug withdrawal is the first step in the treatment of toxicity. However, should neurotoxicity develop or persist despite of this, haemodialysis would remove the drug more effectively than peritoneal dialysis.[5]

Local Situation

As of 3 November 2022, HSA has received 14 adverse event (AE) reports of neurotoxicity or where patients experienced symptoms suggestive of neurotoxicity that were associated with the use of acyclovir and valacyclovir. The AEs included dizziness, headache, confusion, stupor, abnormal thinking, delirium, hallucinations, slurred speech, encephalopathy, dyskinesia, ataxia, and cerebellar syndrome in patients who were treated with acyclovir or valacyclovir. Where stated, the indications for acyclovir and valacyclovir were cytomegalovirus (CMV) prophylaxis in a post-renal transplant patient, and treatment for herpes zoster and herpes simplex. The median age was 61 years old (range 32 to 86 years old). Of the 14 cases, four patients were hospitalised. Five of the patients were reported to have recovered while nine of the patients had unknown outcomes at the point of reporting. Neurological effects such as dizziness, confusion, hallucinations, agitation, seizures, encephalopathy etc. are known AEs and listed in the package inserts of locally registered acyclovir and valacyclovir-containing products. These events are generally reversible. Under the 'Warnings and precautions' section, it is indicated that elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects.[6,7]

Conclusion

Healthcare professionals are encouraged to be vigilant in considering the renal function of patients when prescribing acyclovir and valacyclovir as seen in these two case reports. Healthcare professionals are also reminded to report suspected drug-induced AEs such as neurotoxicity AEs to the Vigilance and Compliance Branch of HSA.

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ANSWER TO AE CASE IN FOCUS 2: TEST YOURSELF

The allergic reactions are triggered by the patient's immune response to cow's milk protein present in the probiotics.

Cow's milk allergy

A review of the ingredient list of the probiotic product showed that it contained milk powder, a known food allergen for the patient (Figure 1). Cow's milk protein may also be labelled as casein, whey, lactoglobulin, lactoferrin, and colostrum in food and health supplements. Refer to Figures 2-4 for examples of the product labels of probiotics and other supplements which contain cow's milk protein. Can you spot the allergen in the labels?

In Singapore, the prevalence of cow's milk allergy in children is 0.51% based on a standardised questionnaire study of over 4,000 children at well-baby visits.[1] In a retrospective review of over 300 Singaporean children with cow's milk allergy, the most common presentation was a cutaneous reaction (angioedema, rash) in 92.4% of the patients.[2] Although most reactions are mild, cow's milk allergy can be severe and life-threatening. About 1 in 20 (5.1%) of cow's milk allergic children experienced milk anaphylaxis at least once in their lifetime.[2] Cow's milk was the third most common cause of food anaphylaxis presenting to the emergency department in a multi-center study involving Singapore children.[3] The prevalence of cow's milk allergy in adults is not well reported and is estimated to range from 0.1 to 0.3%.[4]

Administration of milk proteins, even at a low dose, puts the patient at risk of severe, iatrogenic reactions. Special attention should be paid to probiotics and other health supplements such as colostrum which may contain cow's milk protein. A number of probiotic products including TS6, Vivomixx and Duolac Duo D-Drops have included milk powder or milk protein under the ingredient list or carry a cautionary statement that it may contain traces of milk or milk derivatives.

As of 31 October 2022, HSA has received 35 reports of allergic reactions in children and adults (aged 8 months to 75 years) with probiotic products, including three reports of anaphylaxis. Milk allergies were reported in five patients aged 16 months to 7 years (14% of the reports). Two of these patients experienced anaphylaxis and the remaining three developed skin flushing accompanied with abdominal pain, angioedema with urticaria and perioral rash.

In our case, the situation may have been compounded by other factors: 1) milk allergy was not at the forefront of attention when the patient sought medical attention for unrelated illness; 2) the patient had tolerated milk-free probiotics in the past, giving the caregivers and physicians a false sense of security when trying a new brand, which unfortunately contained milk protein; 3) the probiotics were dispensed as individual sachets, without the full ingredient list, making it difficult for staff and caregivers to verify the absence of milk protein; 4) intercurrent illness is a co-factor for anaphylaxis.

Conclusion

Severe allergic reactions may occur if patients who are allergic to food consume health products containing food allergens. It is important to be vigilant and check the product labels for the presence of cow's milk protein, particularly in probiotics and other health supplements. Healthcare professionals may wish to consider strengthening the medication/dispensing label to carry a warning statement on the presence of milk protein in these products, when dispensing individual sachets without the ingredient list.

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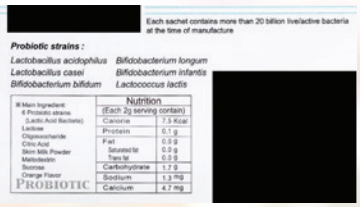
[redacted]
Each sachet contains more than 20 billion live/active bacteria at the time of manufacture
Probiotic strains :
Lactobacillus acidophilus
Lactobacillus casei
Bifidobacterium bifidum
Bifidobacterium longum
Bifidobacterium infantis
Lactococcus lactis
Nutrition
PROBIOTIC
[redacted]

Figure 1. Product label with the ingredient list of causative probiotics.

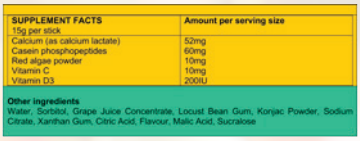
SUPPLEMENT FACTS
Amount per serving size
15g per stick
Calcium (as calcium lactate) 52mg
Casein phosphopeptides 60mg
Red algae powder 10mg
Vitamin C 10mg
Vitamin D3 200IU
Other ingredients
Water, Sorbitol, Grape Juice Concentrate, Locust Bean Gum, Konjac Powder, Sodium Citrate, Xanthan Gum, Citric Acid, Flavour, Malic Acid, Sucralose

Figure 2. Product label showing probiotics and other supplements with cow's milk protein - labeled as casein

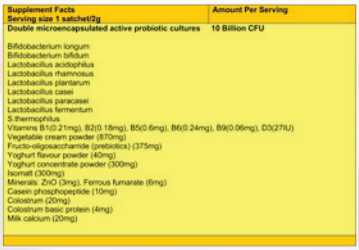
Supplement Facts
Amount Per Serving
Serving size 1 satchet/2g
Double microencapsulated active probiotic cultures 10 Billion CFU
Bifidobacterium longum
Bifidobacterium bifidum
Lactobacillus acidophilus
Lactobacillus rhamnosus
Lactobacillus plantarum
Lactobacillus casei
Lactobacillus paracasei
Lactobacillus fermentum
S.thermophilus
Vitamins B1(0.21mg), B2(0.18mg), B5(0.6mg), B6(0.24mg), B9(0.06mg), D3(27IU)
Vegetable cream powder (870mg)
Fructo-oligosaccharide (prebiotics) (375mg)
Yoghurt flavour powder (40mg)
Yoghurt concentrate powder (300mg)
Isomalt (300mg)
Minerals: ZnO (3mg), Ferrous fumarate (6mg)
Casein phosphopeptide (10mg)
Colostrum (20mg)
Colostrum basic protein (4mg)
Milk calcium (20mg)

Figure 3. Product label showing probiotics and other supplements with cow's milk protein - labeled as colostrum, yoghurt

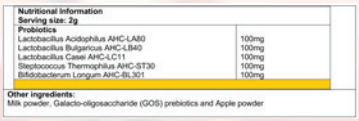
Nutritional Information
Serving size: 2g
Probiotics
Lactobacillus Acidophilus AHC-LA80 100mg
Lactobacillus Bulgaricus AHC-LB40 100mg
Lactobacillus Casei AHC-LC11 100mg
Streptococcus Thermophilus AHC-ST30 100mg
Bifidobacterium Longum AHC-BL301 100mg
Other ingredients:
Milk powder, Galacto-oligosaccharide (GOS) prebiotics and Apple powder

Figure 4. Product label showing probiotics and other supplements with cow's milk protein - labeled as milk powder

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