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ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Health Product Safety Information Summary

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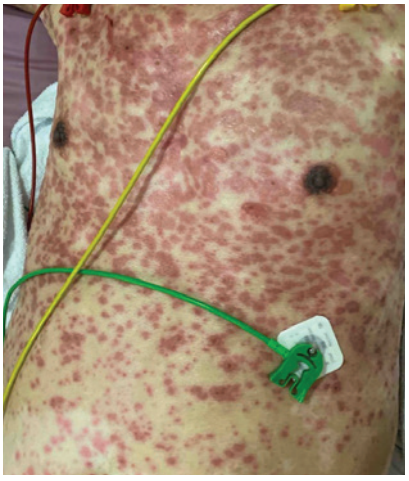
This is a case of a Chinese male in his 60s, with a known retrovirus infection, who presented with an acute onset of painful rashes associated with mucosal involvement. He had consulted a general practitioner, three weeks ago, for pain over his right elbow and was prescribed allopurinol 300mg daily for 20 days, etoricoxib 120mg daily for five days, and colchicine 500mcg TDS for five days. He had not taken any new medication in the last six months.

On examination, he had multiple dusky erythematous lesions on the face, trunk, back, and limbs. Additionally, there were small tense vesicles and bullae on the anterior chest, bilateral conjunctival erythema, erosions on the lips and the glans of the penis. About 50% of his total body surface area (BSA) was involved, and Nikolsky's sign was positive.

What could have caused the rash in this patient?



AE Case in Focus 2: Test Yourself

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This is a case of a Chinese male in his 60s, who had been taking simvastatin 20 mg daily for 10 years, followed by atorvastatin 40 mg daily for five years, for hyperlipidaemia. He had a history of hypertension, diabetes mellitus, ischaemic heart disease, gout and idiopathic left central serous retinopathy. His renal function and creatine kinase (CK) level were normal at the start of simvastatin treatment. He was switched to atorvastatin and remained well for the first five years of the new treatment.

The patient presented with an acute onset of myalgia and proximal myopathy in the week leading up to his admission. He reported difficulties in combing his hair and standing up from a seated position. He was referred to a rheumatologist because his CK levels was 6,000-8,000 international units (IU)/L (Reference range: 40-210 IU/L).

What was the likely cause of the musculoskeletal symptoms in this patient? What treatment options were available for his hyperlipidaemia?

HSA participated in WHO-UMC #MedSafetyWeek 2023 global social media campaign on adverse event reporting

The Health Sciences Authority (HSA) was one of 88 regulatory agencies and organisations that participated in the annual #MedSafetyWeek campaign[1] organised by Uppsala Monitoring Centre, the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring this year. This global social media campaign aimed to raise awareness of the importance of reporting adverse effects from medicines. The theme this year was “Who can report” and focused on how patients, pharmacists and doctors contribute to pharmacovigilance.

During the period from 6 to 12 November 2023, HSA posted animations on our social media platforms Twitter[2], LinkedIn[3] and YouTube[4], highlighting that adverse effects from medicines can happen unexpectedly, at any time and any place, and encouraged patients and caregivers to report the adverse effects to their doctor or pharmacist. Reporting of suspected adverse effects from medicines helps improve patient safety as it enables HSA to detect and investigate any potential safety issues arising from the use of the medicines in Singapore.

HSA also collaborated with Pharmaceutical Society of Singapore and Health Promotion Board which posted the animations on their social media platforms to increase outreach during this week-long campaign.

Healthcare professionals are encouraged to report suspected adverse effects in their patients to HSA. Visit https://www.hsa.gov.sg/adverse-events to report adverse events. Read more about how your report can enhance the safety of medicines at https://www.hsa.gov.sg/consumer-safety/articles/details/AEreporting-medicinesafety.

Follow us on Twitter https://twitter.com/HSAsg to view the series of animations for #MedSafetyWeek and for the latest happenings.

Source of photo: https://twitter.com/HSAsg

References

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4. HSA YouTube https://youtube.com/shorts/6coTI-QUu-w

Dear Healthcare Professional Letters on safety concerns

Scan/click on QR code

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of 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 2023.

Isotretinoin and risk of psychiatric disorders and sexual dysfunction

Key Points

- Psychiatric disorders and sexual dysfunction have been reported with the use of isotretinoin. Based on HSA's review of the available evidence, it is difficult to definitively ascertain causality due to limited and conflicting evidence
- Healthcare professionals may, nevertheless, wish to consider counselling and screening their patients for depressive symptoms or other psychiatric adverse effects when prescribing isotretinoin, and refer them to relevant specialists for further assessment, if necessary
- Healthcare professionals may refer to available Medication Information Leaflets (MILs) on isotretinoin during medication counselling to facilitate the communication of isotretinoin use and its adverse effects to patients and/or caregivers

Isotretinoin is a systemic oral retinoid that has been registered in Singapore since 1990. Currently, there are four brands registered, namely Acnotin (Goldplus Universal Pte Ltd), Nimegen (Zyfas Pharma Pte Ltd), Oratane (Apex Pharma Marketing Pte Ltd) and Roaccutane® (Roche Singapore Pte Ltd). It is indicated for the treatment of severe forms of acne (nodulo-cystic forms) and acne which has failed to respond to other therapies. The use of isotretinoin in paediatric patients less than 12 years of age has not been studied. Careful consideration should be given to patients aged 12 to 17 years who are being treated for severe recalcitrant nodular acne, especially for those with known metabolic or structural bone disease.

Psychiatric disorders and sexual dysfunction have previously been reported with the use of isotretinoin. HSA had reviewed the evidence on these associations in 2018 and 2017, respectively, and concluded that a definitive causal relationship could not be established due to limitations in the available data then. Nevertheless, as the role of isotretinoin in the development of psychiatric and sexual adverse events could not be ruled out, the local package inserts (PI) of isotretinoin products had been strengthened to include safety information on both risks.

Since our last review, new information has emerged, including published literature and actions taken by international drug regulatory agencies. This led HSA to re-evaluate whether the existing safety measures should be further strengthened. Based on the current available information, HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), has concluded that the benefit-risk profile of isotretinoin remains favourable for its approved indications and the current product labelling is sufficient to mitigate both safety concerns.

Published literature

1) Isotretinoin and risk of psychiatric disorders

The association between isotretinoin and the risk of psychiatric disorders, particularly depression, has been investigated in several studies, but the results have been inconsistent and conflicting.[1] Moreover, some studies have suggested that the risk of psychiatric disorders may be confounded by factors such as one's underlying acne condition, acne severity, and physical symptoms induced by the prescribed acne medications (e.g., headache).[2,3] Patients with severe acne may be particularly vulnerable to experiencing mental health symptoms triggered by acne-related psychosocial stress, low self-esteem, or acne flare-ups, especially among those with limited coping and emotional resilience. A study conducted by *Paljarvi et al. (2022)* found that isotretinoin was associated with a lower incidence of adverse neuropsychiatric outcomes compared to oral antibiotics, which are typically prescribed for patients with moderate to severe acne.[3] Additionally, there have been other published studies supporting an improvement in the quality of life or symptoms of anxiety and depression with isotretinoin treatment.[4,5]

2) Isotretinoin and sexual dysfunction

The available evidence on the potential association between isotretinoin and sexual dysfunction, such as erectile dysfunction and decreased libido, is limited to case reports.[6] Mental health issues arising from the underlying acne condition may also confound the relationship between isotretinoin and sexual dysfunction.[7] Furthermore, several studies have shown that adolescents, an age group that is prescribed isotretinoin, commonly experience sexual distress due to the complex interplay of physical, social, and emotional factors (e.g., low sexual esteem and anxiety) that are typical during this developmental stage.[8]

International situation

In 2019, the UK Medicines and Healthcare products Regulatory Agency's (MHRA) advisory committee, the Commission on Human Medicines (CHM), endorsed an independent review by the Isotretinoin Expert Working Group (IEWG) to address concerns raised by patients, families, and other stakeholders regarding the potential adverse effects of isotretinoin on mental health and sexual function when used for acne treatment. The review aimed to evaluate the impact of these adverse effects on the balance of benefits and risks of isotretinoin treatment. The CHM's review findings were published in April 2023, and their recommendations included warnings on the potential risk of psychiatric and sexual disorders and the need of patient counselling in isotretinoin product labels, improvement in their assessment and monitoring, and additional oversight of treatment initiation for patients under 18 years old.[9] These new safety measures and supporting materials were implemented by the UK MHRA on 31 October 2023, and healthcare professionals were advised to integrate them into their clinical practice to strengthen the safe use of isotretinoin.[10]

Other international drug regulatory agencies[a] had also previously reviewed the risks of psychiatric disorders and sexual dysfunction with isotretinoin between 2016 to 2018, and most of them had not imposed safety measures beyond product information labelling to mitigate these risks. At present, no additional safety measures have been implemented by these agencies in response to the UK MHRA's regulatory actions.

[a] *US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, Australia Therapeutic Goods Administration (TGA)*

Local situation

Based on the local sales data, the estimated patient exposure to isotretinoin has remained relatively stable between January 2019 and June 2023, ranging from approximately 3,500 to 4,500 patient-years. Given its long history of use in the local market, there were few local reports of suspected psychiatric disorders and sexual dysfunction associated with isotretinoin. Of the 65 local adverse event reports received for isotretinoin between 1999 to 2023, three were related to psychiatric disorders (depression, psychotic disorder, and suicidal ideation), while one reported erectile dysfunction. These reports generally had limited information or were confounded by the patients' medical history which precluded a meaningful causality assessment. However, we cannot rule out the possibility of under-reporting of these adverse events.

The local PIs of isotretinoin products currently already contain warnings on psychiatric disorders such as depression, anxiety, mood alterations, psychotic disorders and suicidal ideation. Sexual dysfunction, including erectile dysfunction and decreased libido, are also listed in the local PI as adverse events reported in the post-market setting. Patient educational materials for isotretinoin are available on publicly accessible platforms, including the Medication Information Leaflets (MILs) on HealthHub.[11] These MILs provide a brief overview on the administration of isotretinoin and its potential adverse effects. They have highlighted the rare but serious adverse effect of mood changes including depression which require immediate medical advice.

HSA's assessment and advisory

HSA, in consultation with its PVAC, has assessed that the benefit-risk profile of isotretinoin remains favourable and the warnings and safety information in the local PIs of isotretinoin products are sufficient to manage the risks of psychiatric disorders and sexual dysfunction. Nevertheless, it would be relevant to remind healthcare professionals who are prescribing isotretinoin of these potential risks and the relevant measures to be taken.

To allow for prompt detection and management of these adverse effects, healthcare professionals may wish to consider counselling and screening their patients for depressive symptoms or other psychiatric adverse effects when prescribing isotretinoin. They may also consider referring their patients to the relevant specialists for further assessment, if necessary. Healthcare professionals may refer to the available MILs on isotretinoin during medication counselling to facilitate the communication of isotretinoin use and its adverse effects to patients and/or their caregivers.

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11. *https://www.healthhub.sg/a-z/medications/isotretinoin*

AE Case in Focus 1: Test Yourself

A Chinese male in his 60s, with a known retrovirus infection, presented with an acute onset of painful rashes associated with mucosal involvement which started three days ago. He had consulted a general practitioner three weeks ago for pain over his right elbow and was prescribed allopurinol 300mg daily for 20 days, etoricoxib 120mg daily for five days, and colchicine 500mcg TDS for five days. He had not been taking his anti-retroviral treatment or any other new medication in the last six months.

On examination, he had multiple dusky erythematous lesions on the face, trunk, back, and limbs. Additionally, there were small tense vesicles and bullae on the anterior chest (Figure 1), bilateral conjunctival erythema, crusted haemorrhagic erosions on the lips (Figure 2), and erosions on the glans of the penis. About 50% of his total body surface area (BSA) was involved and Nikolsky's sign was positive.

What could have caused the rash in this patient?

Answers can be found on page 6.

HSA would like to thank Dr Wu Xiaotian, Senior Resident, Department of Dermatology, Singapore General Hospital and Dr Heng Yee Kiat, Senior Consultant, National Skin Centre, for their contributions to this article.

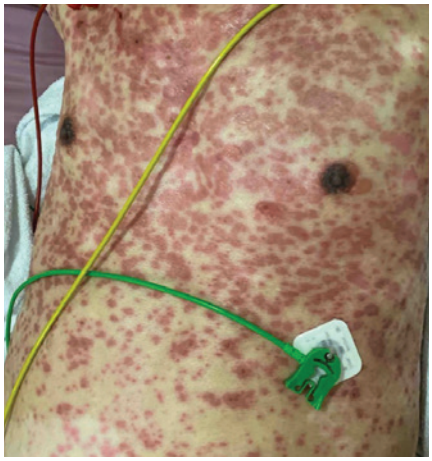

Figure 1. Dusky erythematous legions admixed with small tense vesicles and bullae on the anterior chest

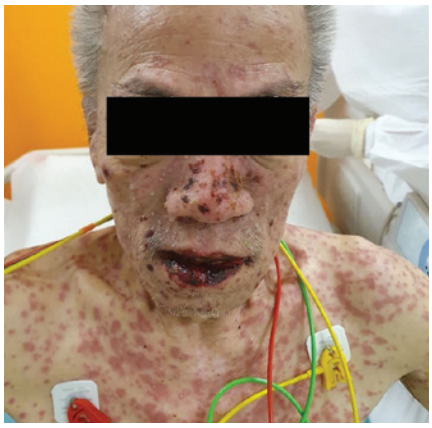

Figure 2. Erosions over both the upper and lower lip with overlying haemorrhagic crust.

Severe cutaneous adverse reaction reports with modafinil and armodafinil

Key Points

- HSA has received several reports of severe cutaneous adverse reactions (SCARs) with the use of modafinil and armodafinil. The reporting rate of Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson syndrome (SJS) associated with modafinil use worldwide exceeds the background incidence rate. Given that three cases of SJS have been reported locally despite the low usage of modafinil and armodafinil, this safety concern may warrant closer monitoring
- Healthcare professionals are advised to consider the possibility of SCARs, including SJS, in patients presenting with prodromal symptoms such as flu-like symptoms, mouth ulcers, sore throat and conjunctivitis

HSA has received reports of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), with the use of modafinil and armodafinil. The patients had obtained these medicines from friends or illegal street peddlers.

Modafinil and armodafinil are used for the treatment of conditions that involve excessive somnolence such as narcolepsy and obstructive sleep apnoea.[1] Both modafinil and armodafinil are not registered in Singapore currently but they may be imported and supplied locally under the special access route (SAR).[2]

Stevens-Johnson syndrome with modafinil and armodafinil

1) Local situation

As at 31 October 2023, HSA has received nine AE reports with modafinil and armodafinil. Seven reports (77.8%) were dermatological/cutaneous reactions*, and of these three reports were SJS. The remaining two reports described increased paranoia and giddiness. From the available information, four patients had obtained their medicines from friends or illegal street peddlers and three of them were self-medicating to stay alert for work. The three reports of SJS involved individuals in their thirties; two were males, and one was a female. The date of onset of SJS ranged from one day to over one month. Modafinil was reported as the suspected drug in two cases and armodafinil in the third case.

** One report each of generalised pruritic rash, angioedema, skin and oral ulcers, fixed drug eruption presented as oral erosions and three reports of SJS.*

2) Clinical trial findings and overseas reports

The incidence of SJS with modafinil and armodafinil is not well established. In clinical trials of modafinil, the incidence of rash resulting in discontinuation was approximately 0.8% (13 per 1,585) in paediatric patients (age <17 years). These reports included one case of possible SJS and one case of apparent multi-organ hypersensitivity reaction.[3]

Rare cases of serious or life-threatening rash, including SJS, Toxic Epidermal Necrolysis (TEN), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) have been reported in worldwide post-marketing experience with modafinil and armodafinil.[3,4] The reporting rate of TEN and SJS associated with modafinil use worldwide exceeds the background incidence rate.[3] Estimates of the background incidence rate for these serious skin reactions in the general population range between 1 to 2 cases per million-person years.[3] Given that three cases of SJS have been reported locally despite the low usage of modafinil and armodafinil, this safety concern may warrant closer monitoring.

Conclusion

HSA had issued two press releases[5] to alert the public on serious adverse reactions, including SJS, with modafinil and armodafinil. The first press release was issued in 2018 and reported the first case of SJS. The second press release was issued more recently, in November 2023, following the receipt of three serious reports (2 SJS and 1 fixed drug eruption requiring hospitalisation) over a three-month period.

Healthcare professionals are advised to consider the possibility of SCARs in patients presenting with prodromal symptoms such as flu-like symptoms, mouth ulcers, sore throat and conjunctivitis. Please report any adverse events, including SCARs, suspected with these medicines to the Vigilance and Compliance Branch of HSA. Information on the source of supply, if available, may be included if healthcare professionals are aware that patients had obtained the medicines from unauthorised sources.

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5. *HSA Press Releases: https://go.gov.sg/hsa-press-releases*

AE Case in Focus 2: Test Yourself

A Chinese male in his 60s had been taking simvastatin 20 mg daily for 10 years, followed by atorvastatin 40 mg daily for five years, for hyperlipidaemia. He also had a history of hypertension, diabetes mellitus, ischaemic heart disease (IHD), gout and idiopathic left central serous retinopathy. His renal function and creatine kinase (CK) level were normal at the start of simvastatin treatment. He tolerated simvastatin well, and thus no CK levels were repeated prior to switching to atorvastatin. He denied any myalgia nor muscle weakness after switching medications and remained well for the first five years while on atorvastatin.

The patient presented with an acute onset of myalgia and proximal myopathy in the week leading up to his admission. He reported difficulties combing his hair and standing up from a seated position. He was referred to a rheumatologist because of a CK elevation of 6,000-8,000 international units (IU)/L (Reference range: 40-210 IU/L)

What was the likely cause of the musculoskeletal symptoms in this patient? What treatment options were available for his hyperlipidaemia?

Answers can be found on page 7.

HSA would like to thank Clinical Assistant Prof Anindita Santosa, Consultant, Changi General Hospital for co-authoring this article with HSA and Adj Assoc Prof Bernard Thong Yu Hor, Rheumatology Department, Tan Tock Seng Hospital for his guidance.

Answer to AE Case in Focus 1: Test Yourself

The patient had toxic epidermal necrolysis (TEN) secondary to allopurinol, prescribed for his right elbow pain which he experienced for the first time. There was no known prior diagnosis of gout in the patient's medical records, and no gouty tophi or tophus was found on clinical examination. Tests done at the hospital revealed that his uric acid level was not elevated. He was tested for HLA-B*5801 and the results was negative. Due to the extensive skin involvement, he was transferred to the Burns Centre at the Singapore General Hospital, where he had a prolonged stay.

Indications for urate lowering therapy with allopurinol for gout

The local Agency for Care Effectiveness (ACE) Clinical Guidance (ACG)[1] on gout management recommends initiating urate-lowering therapy (ULT) for patients with an established diagnosis of gout when they meet any of the ULT treatment criteria. The ACG also recommends to consider starting the patient with allopurinol, as long as physicians are aware of the potential adverse effects with this medication, especially the risk of severe cutaneous adverse reactions (SCARs). The above recommendations are in line with guidelines by other international institutions such as the American College of Rheumatology.[2]

Allopurinol-induced SCARs

SCARs associated with allopurinol include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN). The incidence of allopurinol-induced SCARs ranges from 1.6 to 4.68 per 1,000 users in Asian populations.[3-6] The consequences of allopurinol-induced SCARs can be severe, leading to significant morbidity, mortality, and lifelong complications.

1) *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)*

DRESS presents as a generalised rash, typically two to six weeks after initiation of allopurinol.[7] There is often involvement of the face, sometimes with marked oedema and occasional pustulation. The patient may be systemically unwell with fever and lymphadenopathy. Laboratory abnormalities include peripheral eosinophilia, presence of atypical lymphocytes in the blood, abnormal liver function tests (can be hepatocellular or cholestatic or mixed picture), and elevated creatinine levels. Other organs such as the heart, the lungs and the pancreas may be affected as well, with significant resultant morbidity and mortality.

2) *Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN)*

SJS/TEN presents with mucositis and a painful, dusky, erosive eruption with a typical latency of one to four weeks after exposure to allopurinol.[8] There may be prodromal symptoms of a flu-like illness e.g., sore throat. The condition can progress rapidly with denudation of large areas of the skin and potential complications of fluid and electrolyte imbalances, renal failure and secondary infection, resulting in a high risk of mortality.

Following the acute phase of the SCAR, patients may also develop severe lifelong sequelae, such as autoimmune thyroiditis following DRESS and corneal scarring with resultant vision loss following SJS/TEN. Many of these patients develop significant psychological sequalae as well[9], experiencing depression, post-traumatic stress disorder (PTSD) like symptoms, and anxiety surrounding the initiation of any new medication.

Risk factors for allopurinol-induced SCARs

Several risk factors increase the likelihood of developing allopurinol-induced SCARs, such as renal impairment, elderly age, high starting dose of allopurinol[10], rapid dose escalation, and the presence of the HLA-B*5801 allele.[1]

Local situation

From January 2019 to September 2023, HSA received 505 reports of SCARs associated with health products (Figure 3), of which 65 were associated with allopurinol (Figure 4). Not all the cases reported age, renal function of the patient and prescribed dose of allopurinol. Of the 59 allopurinol cases where age was reported, 39 (66%) were 60 years and above. The renal function of the patients was reported in 35 cases, of which 18 (51%) had renal impairment. Of the 29 cases where the dose of allopurinol was reported, 16 (55%) were prescribed daily doses of 100mg or below while the remaining 13 (45%) cases were prescribed doses of 100mg to 300mg/day. In four cases, the SCARs occurred after doses were increased from the initial 100mg, with increments ranging from 150mg to 300 mg. Of the 15 patients who were HLA-B*5801 genotyped, 11 (73%) tested positive for the allele. All 15 patients were tested after they experienced the SCAR.

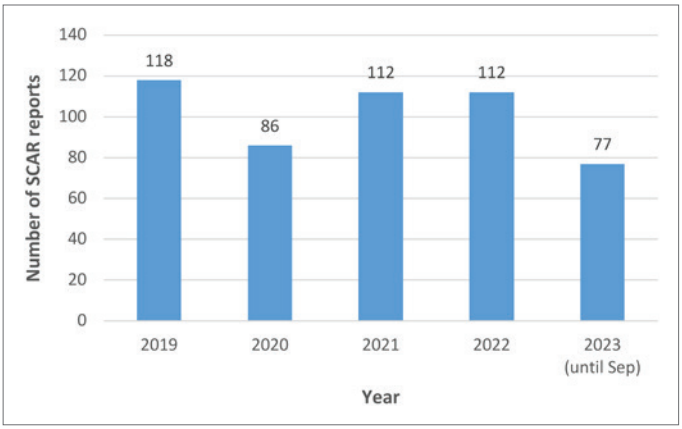

Figure 3. Number of SCAR reports received for health products from January 2019 to September 2023.

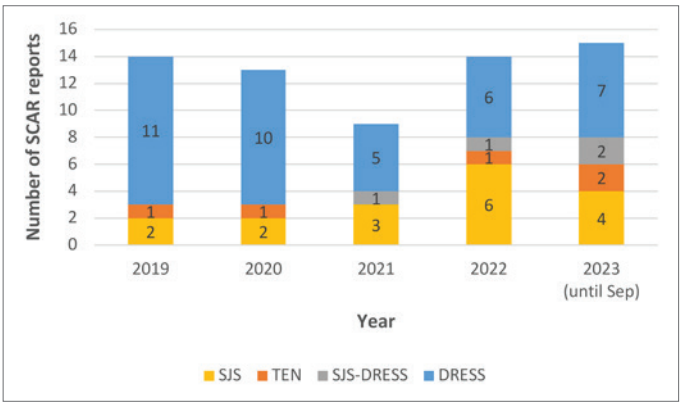

Figure 4. Number of SCAR reports associated with allopurinol from January 2019 to September 2023.

Guidance on SCAR risk mitigation

Healthcare professionals are reminded of the following[1]:

- Carefully assess the suitability of the patient for allopurinol therapy and consider the risk factors in patients starting on allopurinol
- Mitigate the risk of SCAR development by addressing the risk factors where possible e.g., by starting allopurinol at a low dose and slowly titrating upwards
- Consider HLA-B*5801^ genotyping for patients who have pre-existing risk factors for allopurinol-induced SCAR such as renal impairment and older age, to identify those who are at a greater risk of allopurinol-induced SCAR
- Consider and discuss with patients the potential benefits

and costs of HLA-B*5801 testing so that patients are able to make informed decisions regarding their treatment
- Maintain clinical vigilance and monitor patients closely for early signs and symptoms of SCARs

While it is possible for SCAR to develop despite a negative HLA-B*5801 result, as was the case of our patient, the high negative predictive value of the HLA-B*5801 test (close to 100%) could identify the majority of patients who are at a lower risk of developing allopurinol-induced SCARs. HLA-B*5801 genotype testing is available at the laboratories listed in Table 1.

Table 1. Laboratories in Singapore where HLA-B*5801 genotype testing is available

No.	Laboratory	Address and contact	Website link
1	Molecular Diagnostics Laboratory	Tan Tock Seng Hospital 11 Jalan Tan Tock Seng Singapore 308433 E-mail: Mdl_enquiry@ttsh.com.sg	https://www.ttsh.com.sg/Patients-and-Visitors/Medical-Services/personalised-medicine/Pages/default.aspx
2	DNA Diagnostic & Research Laboratory	KK Women's and Children's Hospital Children's Tower, Basement 1 100 Bukit Timah Road Singapore 229899 Tel: (65) 6394 1395/6 Email: ddrl@kkh.com.sg	https://www.kkh.com.sg/patient-care/areas-of-care/childrens-services/Pages/dna-diagnostic-research-lab.aspx
3	Tissue Typing Laboratory	Health Sciences Authority 11 Outram Road Singapore 169078 Tel: 6213 0632 / 6213 0633 E-mail: HSA_BSG_TPS@hsa.gov.sg	https://www.hsa.gov.sg/about-us/blood-services/transfusion-medicine/hospital-services/tissue-typing-laboratory

Please refer to the respective laboratory's websites for more information.

*^HLA-B*5801 genotype testing prior to initiation of allopurinol is currently not routinely recommended in our local Singaporean population[8] and patients who tested negative for the allele may develop allopurinol-induced SCAR due to other non-genetic risk factors. Hence, close monitoring and clinical vigilance of patients on allopurinol is important.[11]*

Conclusion

Healthcare professionals are reminded to be vigilant of the risk of allopurinol-induced SCARs in patients. Healthcare professionals are encouraged to educate patients starting on allopurinol to recognise early signs and symptoms of SCARs, the importance of prompt drug withdrawal and to seek medical attention at the first sign of rash. Patient educational materials such as the HSA's consumer guide on the safe use of allopurinol[12] and the Patient Education Aid on SCARs in ACE ACG[1] may be used during medication counselling.

Healthcare professionals are encouraged to report any suspected serious adverse reactions related to allopurinol to the Vigilance and Compliance Branch of HSA.

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Answer to AE Case in Focus 2: Test Yourself

What was the likely cause of the musculoskeletal symptoms in this patient?

Investigations were carried out which included an electromyogram (EMG), muscle biopsy, and myositis specific antibody (MSA) profile using an ELISA. The latter was found to be positive for anti-HMG-CoA reductase (anti-HMGCR) antibody and muscle biopsy showed muscle fibre necrosis and regeneration with increased MHC Class I expression and paucity of inflammatory infiltrates, which are suggestive of a necrotising immune-mediated myopathy associated with HMGCR antibody. This led to a diagnosis of statin-induced myositis, and the statin therapy was promptly stopped. His condition improved with treatment with systemic corticosteroids and intravenous immunoglobulin (IVIG). His CK levels improved to 2,600-2,800 IU/L two weeks after his first IVIG infusion and 1,600 IU/L after his second monthly IVIG infusion and a tapering course of prednisolone. His treatment plan included further IVIG infusions in the next six months with a rapid tapering of prednisolone in view of his history of central serous retinopathy.

What were the treatment options available for his hyperlipidaemia?

At the time of presentation, atorvastatin was discontinued. The decision to continue withholding statins was made with the subsequent diagnosis of necrotising immune-mediated myopathy associated with anti-HMGCR. Given the patient's significant cardiovascular risk factors and history of IHD, he was considered for a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

Statins and adverse effects of myopathy and myositis

Statins are widely prescribed medications for managing hyperlipidaemia and reducing the risk of cardiovascular events.

Patients taking statins may experience muscle-related adverse effects. These range from self-limiting myalgias to rare events of rhabdomyolysis and statin-associated immune-mediated necrotising myopathy (IMNM).[1]

Statins can cause myopathy/myositis either as a non-inflammatory, toxic effect which is self-limiting or as a trigger of an autoimmune process. While their presentations can be similar, the difference between the two conditions is the presence of myositis specific autoantibody, necrotising myositis on muscle biopsy, and need for immunosuppressive therapy for IMNM.[1] Please refer to Table 1 for the comparison of characteristics of self-limited statin myopathy and statin-associated IMNM.

Table 1. Characteristics of self-limited statin myopathy and statin-associated immune-mediated necrotising myopathy[1,2,3,4,5,6]

Characteristics	Self-limited statin myopathy*	Statin-associated IMNM
Frequency	Approximately 1 of 10,000 patients treated per year	2 or 3 of every 100,000 patients treated with a statin
Myalgia	Common	Common
Proximal muscle weakness	Uncommon	Common Progressive proximal weakness, especially posterior thigh, medial thigh and gluteal compartments
CK levels	Normal or raised; Myalgia: Normal or <4x upper limit normal (ULN); Myopathy: >4x but <10x ULN Rhabdomyolysis: >10x, can be up to 50x ULN	>10x ULN

Onset	Myalgia and myopathy: following initiation, resolve after discontinuation; Rhabdomyolysis: resolution depends on degree of muscle damage	Frequently delayed by months to years after statin commencement; may appear or persist after statin discontinuation
Anti-HMG-CoA reductase antibody	Absent	Present
Electromyography	May show irritable myopathy	Irritable myopathy
Biopsy	Non-specific	Necrosis, degeneration and regeneration
Treatment	Withdraw statins	Withdraw statins; immunosuppression with glucocorticoid therapy, methotrexate with the option of adding IVIG. Further addition of rituximab if there is inadequate response
Prognosis	Resolution after discontinuation of statins	Progressively worse, usually requiring immunosuppressive therapy for remission

** Includes myalgia, myopathy and rhabdomyolysis*

Local situation

From 2018 to 30 September 2023, HSA has received 43 reports of statin-associated myositis, of which 38 were tested positive for anti-HMGCR antibody. The reports were on the uptrend since 2022, possibly contributed by the availability and increased anti-HMGCR antibody tests being done as part of clinical workup in recent years to better characterise and prognosticate patients presenting with idiopathic inflammatory myopathies (IIM). The median age was 65 years (range is 48 to 81 years). There were more reports in females than males (21 versus 17). Atorvastatin was reported as the suspected drug in the majority of reports (N=34, 79%), followed by simvastatin (N=7, 16%) and rosuvastatin (N=2, 5%), which appears to be in line with its usage in the public healthcare institutions.

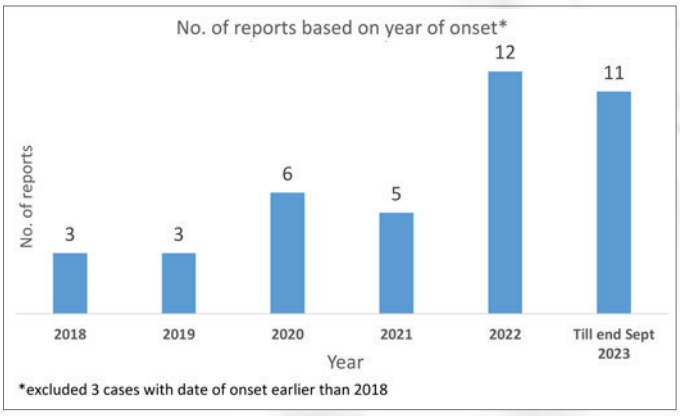

Figure 1. No. of reports of statin-associated myositis received from 2018 to September 2023

Conclusion

According to the National Population Health Survey 2020 conducted from July 2019 to March 2020, the prevalence of hyperlipidaemia among Singapore residents was 39.1%.[7] This was an increase from 35.5% reported in 2017.[7] In view of the place of therapy of statins and the risk of myositis, healthcare professionals are advised on the following:

- *To be vigilant of possible statin-associated myositis when patients present with myopathy symptoms:* The onset of IMNM associated with anti-HMGCR is frequently delayed by months to years after statin commencement and does not typically resolve with statin cessation
- *To consider the following as part of patient monitoring to facilitate diagnosis of potential statin-associated myositis:* Measure the serum CK to establish patient's baseline prior to starting therapy, after dose escalation or when patients present with muscle symptoms. Healthcare professionals may refer to the local clinical guidelines for more details on monitoring patients on statins. Patients may also be advised to report promptly to their doctors if they experience any muscle pain, especially if it is progressive and associated with weakness
- *To document in patient's medical records to prevent future occurrence of the adverse event where possible:* In light of the role that statins play in the pathogenesis of anti-HMGCR IMNM, it is advisable to stop statins when the diagnosis is suspected or has been made. While there remains a lack of evidence for discontinuing, continuing or switching statins, taking into account the clinical significance and seriousness of the adverse reaction, healthcare professionals may wish to consider documenting the diagnosis in a shared repository or electronic database, such as the Critical Medical Information System (CMIS)∞, to prevent re-exposure to statin.

∞ The CMIS is a data repository of a patient's medical history such as allergies and adverse reactions which may be accessible by other healthcare professionals attending to the patient.

Appropriate monitoring, prompt diagnosis, avoidance of re-exposure to statins, and patient education are important in minimising the risks of statin-associated myositis.

References

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5. *J Neuromuscul Dis. 2018; (1): 11-20*
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7. *Statistics Singapore Newsletter Issue 1, 2022*

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