SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually m ore than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

26-06-2025

Saudi Food and Drug Authority (SFDA) – Safety Signal of Pembrolizumab and the Risk of Systemic sclerosis

*The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of **Systemic sclerosis** associated with the use of **Pembrolizumab**. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Pembrolizumab is an immunotherapy drug known as a checkpoint inhibitor, used to treat various cancers. The injection used, either alone or with chemotherapy, and is indicated for conditions such as melanoma (including post-surgical prevention), cutaneous squamous cell carcinoma, non-small-cell lung cancer (NSCLC), head and neck cancer, Hodgkin's lymphoma, primary mediastinal B-cell lymphoma (PMBCL), and other cancer types. [1] Systemic sclerosis is a rare, chronic autoimmune connective tissue disorder characterized by degenerative changes and scarring in the skin, joints, and internal organs and by blood vessel abnormalities. Systemic sclerosis causes an overproduction of collagen and other proteins in various tissues. The cause of systemic sclerosis is not known. [2] The aim of this review is to evaluate the risk of Systemic sclerosis associated with the use of Pembrolizumab and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between Systemic sclerosis and Pembrolizumab use. The search conducted on March 2025.

Results

Case Review: Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs). The WHO database resulted in 14 global case-reports while no local cases found. The authors used signal detection tool (Vigilyze) to retrieve global cases. [3] Authors also applied WHO-UMC causality assessment criteria on all the extracted ICSRs. [4] Among the reported cases, three were assessed as probably or possibly related to Pembrolizumab, while the remaining eleven could not be evaluated due to insufficient information.

Datamining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association. The IC result is (3.0) for this drug/ADR combination which reflects positive statistical association. [4]

Literature: The signal team conducted a literature search to identify publications linking this adverse drug reaction to Pembrolizumab. The search revealed two published articles reporting cases of systemic sclerosis following the use of Pembrolizumab. [5,6]

Conclusion

The weighted cumulative evidence identified from assessed cases, disproportionality analysis and literature are suggestive for causal association between Pembrolizumab and Systemic sclerosis. Health care professionals and health regulators must be aware of the potential risk in drug recipients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1- Pembrolizumab injection: Medlineplus Drug Information (no date) MedlinePlus. Available at: https://medlineplus.gov/druginfo/meds/a614048.html

2- Nevares, A.M. (2022). Systemic Sclerosis. [online] MSD Manual Consumer Version. Available at: https://www.msdmanuals.com/home/bone-joint-and-muscle-disorders/autoimmune-disorders-of-connective-tissue/systemic-sclerosis

3- Vigilyze.who-umc.org. 2025. [online] Available at: https://vigilyze.who-umc.org/

4- World Health Organization WHO (2013). WHO-UMC system for standardised case causality assessment. Available at https://www.who.int/publications/m/item/WHO-causality-assessment

5- Barbosa, N.S., Wetter, D.A., Wieland, C.N., Shenoy, N.K., Markovic, S.N. and Uma Thanarajasingam (2017). Scleroderma Induced by Pembrolizumab: A Case Series. Mayo Clinic Proceedings, 92(7), pp.1158–1163. doi: https://doi.org/10.1016/j.mayocp.2017.03.016

6- Alkilany, R. and Ballou, S. (2020). Pembrolizumab induced scleroderma. Discussion of Clinical Cases, 6(4), p.6. doi: https://doi.org/10.5430/dcc.v6n4p6