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 more 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"

06-03-2024

Saudi Food and Drug Authority (SFDA) – Safety Signal of Nivolumab and the Risk of Capillary Leak Syndrome

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

Introduction

Nivolumab is a medication used to manage and treat metastatic melanoma and several other tumors. It is a monoclonal antibody that targets the anti-PD1 receptor, an immune checkpoint. [1] Systemic capillary leak syndrome (SCLS) causes fluid and proteins to leak out of tiny blood vessels (capillaries) into surrounding tissues. This may lead to hypotension, hypoalbuminemia, and thickened blood due to a decrease in plasma volume (hemoconcentration). [2] The aim of this review is to evaluate the risk of Capillary leak syndrome associated with the use of Nivolumab 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 Capillary leak syndrome and Nivolumab use. The search conducted on January 2024.

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 25 global case-reports while no local cases found. The authors used signal detection tool (Vigilyze) to retrieve all reported global cases. [3] Authors also applied WHO-UMC causality assessment criteria on ICSRs with completeness score 0.6 and above (n=10). [4] Among them, 7 cases of Capillary leak syndrome were possibly linked to Nivolumab while the remaining 3 cases assessed as unlikely.

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 (2.9) for this drug/ADR combination which reflects strong positive statistical association. [4]

Literature: The signal team searched the literature to find related publications linking this ADR to Nivolumab. The search showed two published case-reports of Capillary leak syndrome following the use of Nivolumab [5,6]

Conclusion

The weighted cumulative evidence identified from assessed cases, disproportionality analysis, and literature are sufficient to suggest causal association between Nivolumab and Capillary leak syndrome. 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- Rendon A, Rayi A. Nivolumab. [Updated 2022 Dec 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK567801/ [Accessed: 08/01/2024].

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5- Céline Lescure, Alain Lescoat, Alexandre Salé, Yann Bazin, Loïg Duvergé, Benoit Desrues, Hervé Léna, Systemic Capillary Leak Syndrome (Clarkson's Disease) as a Complication of Anti–Programmed Death 1 Immunotherapy, Journal of Thoracic Oncology, Volume 14, Issue 6, 2019, Pages e131-e132, ISSN 1556-0864, https://doi.org/10.1016/j.jtho.2019.02.003.

6- Polishchuk, I., Yakobson, A., Zemel, M., A Sharb, A., Shalata, W., Rosenberg, E., & Kian, W. (2021). Nivolumab-induced systemic capillary leak syndrome as an ultra-rare life-threatening phenomenon of late toxicity and intravenous immunoglobulin efficacy. Immunotherapy, 13(10), 807-811.