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"

3-1-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Nivolumab and the Risk of Hypoparathyroidism

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

Introduction Nivolumab is a fully human immunoglobulin (Ig) G4 monoclonal antibody directed against the negative immunoregulatory human cell surface receptor programmed death-1 (PD-1, PCD-1,) with immune checkpoint inhibitory and antineoplastic activities [1,2]. Hypoparathyroidism occurs when there is destruction of the parathyroid glands (autoimmune, surgical), abnormal parathyroid gland development, when PTH is insufficient hypocalcemia develops and this may be associated with a spectrum of clinical manifestations [3]. The aim of this review is to evaluate the risk of Hypoparathyroidism and the association with the use of Nivolumab and to suggest regulatory recommendations if required.

Methodology Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase) [4], to retrieve related information for assessing the causality between Nivolumab and the Risk of Hypoparathyroidism. the WHO-Uppsala Monitoring Centre (UMC) criteria used as standard for assessing the causality of the reported cases [5]

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 6 global ICSRs as of February 20, 2019. Among all 6 ICSRs, one case reported with positive dechallenge and one with negative dechallenge, after applying WHO-UMC causality assessment two cases resulted in possible association and three were with unlikely association and on case was unclassified.

Data Mining: 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, considering the null value equal to zero. The results of (IC= 2.92) revealed a positive statistical association for the drug/ADR combination, which means "Hypoparathyroidism" with the use of "Nivolumab" have been observed more than expected when compared to other medications available in WHO database.

Literature: Multiple evidences have been found during the literature search (two case-reports).

A case of 61-year-old female with a 2-year history of metastatic small cell lung cancer who had been treated with Nivolumab, few months before patient was admitted with low total serum calcium, ionized calcium, and parathyroid hormone (PTH). The patient was diagnosed with severe hypocalcemia as a result of autoimmune hypoparathyroidism after testing positive for CaSR-activating autoantibodies [6].

Another case report for a 73-year-old man with metastatic melanoma had wide spread metastasis, and begun immunotherapy with concurrent Ipilimumab and Nivolumab 1.5 months ago. At presentation, he was found to be hypocalcemic with undetectable plasma parathyroid hormone. He was admitted for treatment of symptomatic hypocalcemia and was diagnosed with primary hypoparathyroidism [7].

Conclusion

The weighted cumulative evidences identified from the reported cases, data mining and literature are sufficient to support a causal association between Nivolumab and the risk of Hypoparathyroidism. Health regulators and health care professionals must be aware for this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

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:

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6. Paramarajan Piranavan, Yan Li, Edward Brown, E Helen Kemp, Nitin Trivedi; Immune Checkpoint Inhibitor-Induced Hypoparathyroidism Associated With Calcium-Sensing Receptor-Activating Autoantibodies, The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 2, 1 February 2019, Pages 550–556, https://doi.org/10.1210/jc.2018-01151
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