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"

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

*The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of **Cystitis** 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 IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody that selectively blocks the interaction of the PD-1 receptor with its two known programmed death ligands, PD-L1 and PD-L2, disrupting the negative signal that regulates T-cell activation and proliferation [1]. Cystitis is inflammation of the bladder commonly caused by bacterial infection [2]. There is growing evidence of linking Cystitis to certain drugs [3]. The aim of this review is to evaluate the risk of Cystitis associated 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), to retrieve related information for assessing the causality between Nivolumab and the risk of Cystitis [4]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria 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 40 global ICSRs as of January 2021 [4]. The reviewers have selected and assessed the causality for top quality reported cases with completeness score of 0.8 and above (12 ICSRs). Out of 12 assessed ICSRs, five reports revealed probable association with five positive dechallenge reactions [5].

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. The results of (IC= -0.4) revealed a negative statistical association for the drug/ADR combination, meaning "Cystitis " with the use of "Nivolumab" has been observed less than expected compared to other medications available in WHO database [4].

Literature Upon conducting a literature search, multiple evidences found supportive for this signal.

A 50-year-old man with normal urinalysis before administration of seven cycles of Nivolumab. After the seven cycles, urinalysis was significant for pyuria with >100 white blood cells per high power field, mainly neutrophils in urine cytology, was detected. Patient was treated with antibiotic with no recovery. Then, medication was discontinued and patient had positive dechallenge [6].

Another Nivolumab-linked cystitis case of a 60-year-old male patient with positive dechallenge and rechallenge was reported [7]. Furthermore, Cystitis was found to be associated with Nivolumab in a 62-year-old man treated for pulmonary squamous cell carcinoma [7].

Conclusion

The weighted cumulative evidence identified from the reported cases and literature are sufficient to support a causal association between Nivolumab and the risk of Cystitis. Health regulators and health care professionals must be aware of 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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