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 Pembrolizumab and the Risk of Cholestasis

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

Introduction

Pembrolizumab is an antineoplastic agent. It is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. potentiates T-cell responses, including anti-tumor responses [1]. Cholestasis is a liver disease that occurs when the flow of bile from the liver is reduced or blocked. Bile is fluid produced by liver that aids in the digestion of food, especially fats [2]. The aim of this review is to evaluate the risk of Cholestasis associated with the use of Pembrolizumab and 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 Pembrolizumab and the Risk of Cholestasis [3]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 63 global Individual case safety reports (ICSRs) as of November 2021 [4]. The reviewers have selected and assessed the causality for top quality reported cases (33 ICSRs). Out of 33 assessed ICSRs, 18 reports revealed positive association (1 certain, 10 probable and 7 possible) with 14 positive dechallenges [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= 2.2) revealed a positive statistical association for the drug/ADR combination, meaning "cholestasis" with the use of "Pembrolizumab" has been observed more than expected compared to other medications available in WHO database [3].

Literature: This signal was detected from phase 3 double-blind trial entitled (Adjuvant Pembrolizumab after Nephrectomy in Renal-Cell Carcinoma). Cholestasis was one of the identified serious adverse events [5]

Additionally, a case report entitled (Cholestatic Liver Injury Induced by Pembrolizumab in a Patient with Lung Adenocarcinoma) was found in literature. A 48-year-old male patient diagnosed with lung adenocarcinoma. The patient was treated with pembrolizumab as second-line therapy. Eleven days after the second administration of pembrolizumab, he developed cholestatic liver injury [6].

Conclusion

The weighted cumulative evidence identified from the reported cases, data mining and literature are sufficient to support a causal association between pembrolizumab and the risk of cholestasis. 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

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