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"

23-10-2022

Saudi Food and Drug Authority (SFDA) – Safety Signal of Atezolizumab and the Risk of Sclerosing Cholangitis

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

Introduction

Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody belonging to new class of antineoplastic agents called (Immune Check-Points Inhibitors). The drug is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma. PD-L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response [1]. Sclerosing Cholangitis is a chronic progressive cholestatic liver disease, characterized by inflammation and fibrosis of the intrahepatic and/or extrahepatic bile ducts, resulting in diffuse, multi-focal stricture formation [2]. The aim of this review is to evaluate the risk of Sclerosing Cholangitis associated with the use of Atezolizumab 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 Atezolizumab and the risk of Sclerosing Cholangitis [3]. We used the WHO-Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: There was one individual case safety reports (ICSRs) for the combined drug/adverse drug reaction as of September 2022 [3]. The patient from Japan and was treated with Atezolizumab for

lung adenocarcinoma. The reporter missed to report the date of Sclerosing Cholangitis onset and accordingly, the case was considered not assessable due to lack of information necessary to establish temporal relationship between the drug and the ADR [4].

Data Mining: Information component (IC), a tool developed by WHO-UMC to measure the reporting ratio, is used to estimate the disproportionality of the observed and expected reporting rates for drug/adverse drug reaction pairs. Positive IC values indicate a statistical association, whereas negative values indicate a weaker statistical association. The results of (IC= 1.1) revealed that the drug/ADR combination has a positive statistical association. In other words, DIC has been observed more than expected with Atezolizumab compared to other medications in the database [3].

Literature: A 77-year-old woman with adenocarcinoma of the lung was treated with Atezolizumab (1200 mg intravenously) every 3 weeks following tumor progression over chemotherapy and radiation. After 13 cycles of Atezolizumab, the patient was admitted to hospital with a complaint of nausea. Laboratory tests revealed total bilirubin (T-Bil), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (ɤ GTP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels of 2.6 mg/dl, 2837 mg/dl, 864 U/l, 184 mg/dl, and 193 mg/dl, respectively. Atezolizumab treatment was discontinued and she was administered oral Ursodeoxycholic acid; however, her biliary enzyme levels improved poorly and symptoms persisted. CT scan revealed no cholelithiasis or biliary tumor. histopathological findings of the bile biopsy confirmed ring-like fibrosis surrounding the bile duct and inflammatory cell infiltration. Based on the findings, a diagnosis of Atezolizumab-induced secondary Sclerosing Cholangitis established [5].

Conclusion

The weighted cumulative evidence identified from literature and datamining are sufficient to support a causal association between Atezolizumab and the risk of Sclerosing Cholangitis. 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:

1. Hoffmann-La Roche Ltd (2022). Saudi Summary of Product Characteristics (SPC) of Tecentriq- Atezolizumab Available at: https://sdi.sfda.gov.sa/
2. Tischendorf JJ, Hecker H, Kruger M, et al. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. Am J Gastroenterol. 2007 Jan;102(1):107-14.

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