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"

7-9-2020

Saudi Food and Drug Authority (SFDA) – Safety Signal of Rhabdomyolysis Associated with the Use of Pembrolizumab products

The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of ***Rhabdomyolysis*** *associated with the use of* ***Pembrolizumab****. The safety signal has been originated based on detected signal from the Marketing Authorization Holder.*

Background: Pembrolizumab is programmed death receptor-1 (PD-1) blocking antibody. Binding of PD-1 on T-cells to its ligands inhibits T-cell proliferation. Blocking PD-1 with Pembrolizumab releases the inhibition of the immune response of T-cells, including an anti-tumor response. [1] Rhabdomyolysis characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. Creatine kinase levels are elevated, and muscle pain may be present. The severity of illness ranges from asymptomatic elevations in serum muscle enzymes to life-threatening disease associated with extreme enzyme elevations, electrolyte imbalances, and acute kidney injury. [2]

Methodology: on March 3, 2020, the Signal Detection team at Saudi Food and Drug Authority (SFDA) performed a safety review using NPC database, and World Health Organization (VigiBase), along with literature screening to retrieve all related information would be beneficial to assess the causality between Rhabdomyolysis and Pembrolizumab use.

Results:

Cases: Although, The NPC has not received aby report concerning this signal, The WHO database (VigiBase) searched for all individual case Study reports (ICSRs) reported with "Rhabdomyolysis" and "Pembrolizumab" yielded to 59 ICSRs. Initial review revealed that 30 cases were not sufficiently documented for proper medical assessment. However the remaining (29) have been furthered evaluated resulted in thirteen cases with positive dechallenge and three with negative rechallenge and after applying the WHO causality assessment criteria, resulted in five cases with probable association, six cases with possible association, three cases with unlikely association and fifteen unassessable cases due to lack of information. [3]

Literature: During literature search, one case report has been found supporting the association1, 83 year male was diagnosed with lung adenocarcinoma, Pembrolizumab 200 mg was started every 3 weeks. Patient presented with myalgia and lower back pain after 1 week of the second cycle of Pembrolizumab. Then admitted to hospital because he was unable to walk without assistance. He was diagnosed with rhabdomyolysis, a suspected immune-related toxicity. Pembrolizumab discontinued and initiated systemic prednisone Myalgia and ptosis improved within 4 weeks after prednisone administration. [4]

Datamining: The disproportionality between observed and expected reporting rate of drug-adverse drug reaction combination calculated using Information Component (IC). Higher IC value means a strong statistical association between certain medications with the event in comparison to other medications. The combination of Pembrolizumab and Rhabdomyolysis has observed more than expected (IC 0.9) when compared with other medications. [3]

Conclusion:

The weighted cumulative evidences identified from global cases, data mining and published literature are sufficient to support a causal association between Rhabdomyolysis and Pembrolizumab. Therefore, health care professionals should be aware of this safety concern and may consider monitoring any signs or symptoms of Rhabdomyolysis in patients treated with Pembrolizumab.

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- Merck Sharp & Dohme Limited (2018). Saudi Summary of Product Characteristics (SPC) of pembrolizumab. (KEYTRUDA) ®; (retrieved from SFDA database).

2- Marc L Miller, MD. (2018). Clinical manifestations and diagnosis of rhabdomyolysis. Monica Ramirez Curtis (Ed.), Up-To-Date. Retrieved from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-rhabdomyolysis [Accessed 3/3/2020]

3- Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org/#/ [Accessed 3/3/2020]

4- Hamada, S., Fuseya, Y., & Tsukino, M. (2018). Pembrolizumab-Induced Rhabdomyolysis with Myositis in a Patient with Lung Adenocarcinoma. Archivos De Bronconeumología, 54(6), 346–348. doi: 10.1016/j.arbres.2018.01.026