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"

21-9-2021 (Updated)

Saudi Food and Drug Authority (SFDA) – Safety Signal of Aflibercept and the Risk of Fournier's gangrene

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

Introduction

Aflibercept is produced in Chinese hamster ovary (CHO) K1 cells by recombinant DNA technology. It act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Aflibercept in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer (MCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. [1] Fournier gangrene is defined as a polymicrobial necrotizing fasciitis of the perineal, perianal, or genital areas. Impaired immunity (eg, from diabetes) is known to increase susceptibility to Fournier gangrene. Trauma to the genitalia, which can cause a breach in the integrity of epithelial or urethral mucosa, is a frequently recognized mechanism by which bacteria are introduced, subsequently initiating the infectious process. [2]

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 Aflibercept and the risk of Fournier gangrene. [3] WHO-Uppsala Monitoring Centre (UMC) criteria have been used as standard for assessing the causality of the reported cases. [4]

Results

Cases Review: The number of resulted cases for the combined drug/adverse drug reaction are five global ICSRs as of March 2021 [3]. One case was excluded due to duplication. The reviewers have

extracted and assessed the causality for all ICSRs (4 ICSRs). The causality assessment resulted in two probable cases and two unassessable cases.

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 result of (IC= 2) revealed a positive statistical association for the drug/ADR combination, which means "Fournier gangrene" with the use of "Aflibercept" have been observed more than expected when compared to other medications available in WHO database. [3]

Literature: Upon conducting a literature search, multiple relevant studies were found and summarized as below:

A case report of 64 years-old man with stage IV rectosigmoid cancer admitted to the emergency department because of fever and buttock pain. 23 days before admission, the patient has received one cycle of FOLFIRI-aflibercept. A clinical diagnosis of Fournier's gangrene (FG) has been made. He developed Fournier's gangrene with the only identified risk factor being immunosuppression due to chemotherapy. [5] Additionally, Fournier's gangrene may be a class effect of antiangiogenic treatment. There are several case reports of Fournier's gangrene after using anti-angiogenic drugs including Lenvatinib, Regorafenib, Bevacizumab and Ramucirumab. [5,6,7,8]

Conclusion

The weighted cumulative evidences identified from causality assessment of the reported cases, data minig and literature are sufficient to support a causal association between Aflibercept and the risk of Fournier gangrene. 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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