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"

9-8-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Bevacizumab 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 **Bevacizumab.** The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Bevacizumab is a recombinant humanized monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells. It is indicated for metastatic carcinoma of the colon or rectum (mCRC), non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC) epithelial ovarian, fallopian tube and primary peritoneal cancer, cervical cancer and glioblastoma. [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 Bevacizumab 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

Case Review: The number of resulted cases for the combined drug/adverse drug reaction is thirty-five global ICSRs as of March 2021. [3] The reviewers have extracted and assessed the causality for all ICSRs (35 ICSRs). The causality assessment resulted in five probable cases, four possible cases, two unlikely cases and twenty- four cases were not assessable.

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= 3.6) revealed a positive statistical association for the drug/ADR combination, which means "Fournier gangrene" with the use of "Bevacizumab" 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 67 years-old who was admitted to o the emergency department with complaints of increasing buttock pain, scrotal swelling, abdominal discomfort and malaise for several days. After doing the physical examination , comprehensive metabolic panel, blood count and wound cultures, he was admitted to the surgical intensive care unit with a diagnosis of Fournier's gangrene. This case conclude that the patient's Fournier's gangrene was caused by Bevacizumab therapy and further investigation is needed. [5]

An abstract of case report entitled (A Case of Fournier's Gangrene Due to Perforation of Lower Rectal Cancer during Chemotherapy) was found 73 years-old man with unresectable rectal cancer. He was receiving chemotherapy of mFOLFOX6 plus bevacizumab regimen and then he was admitted to the emergency department due to consciousness disorder. A diagnosis of Fournier's gangrene has been made and urgent operation was performed. This case report emphasized on paying attention to Fournier's gangrene during chemotherapy with bevacizumab in patients with lower rectal cancer. [6]

Another abstract of case report of 51-year-old man who underwent abdominoperineal resection for advanced rectal cancer. 58 months later, he was diagnosed with local pelvic recurrence and metastasis to the para-aortic lymph node and both adrenal glands. He received 30 Gy of radiation for analgesia. Chemotherapy (mFOLFOX6 plus bevacizumab) was initiated. After 6 courses of chemotherapy, he was diagnosed with Fournier's gangrene caused by small intestinal perforation. [7]

Conclusion

The weighted cumulative evidences identified from causality assessment of the reported cases, data-mining and literature are sufficient to support a causal association between Bevacizumab 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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2. Emedicine.medscape.com. 2021. Fournier Gangrene: Practice Essentials, Background, Anatomy. [online] Available at: <https://emedicine.medscape.com/article/2028899-overview> [Accessed 3/24/2021].
3. Vigilyze.who-umc.org. 2021. [online] Available at: <https://vigilyze.who-umc.org/> [Accessed 3/24/2021].
4. Uppsala Monitoring Center (UMC) (2021), The use of the WHO-UMC system for standardized case causality assessment; Available at <https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1> [Accessed 3/24/2021].
5. Gamboa, E., Rehmus, E. and Haller, N., 2010. Fournier's Gangrene as a Possible Side Effect of Bevacizumab Therapy for Resected Colorectal Cancer. Clinical Colorectal Cancer, 9(1), pp.55-58.
6. Fukuhisa H, Baba K, Kita Y, et al. 2017. A Case of Fournier's Gangrene Due to Perforation of Lower Rectal Cancer during Chemotherapy. Gan to Kagaku ryoho. Cancer & Chemotherapy,44(10):935-937.
7. Ishida T, Shinozaki H, Ozawa H, et al. 2016. A Case of Fournier's Gangrene Caused by Small Intestinal Perforation during Bevacizumab Combination Chemotherapy. Gan to Kagaku ryoho. Cancer & Chemotherapy. 43(7):909-911.