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"

21-2-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Dolutegravir and the Risk of Hyperglycemia

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

Introduction Dolutegravir is an antiviral agent used in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children over 12 years of age [1]. Hyperglycemia is blood glucose greater than 125 mg/dL while fasting and greater than 180 mg/dL 2 hours postprandial [2]. The aim of this review is to evaluate the risk of Hyperglycemia associated with the use of dolutegravir 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 Dolutegravir and the Risk of Hyperglycemia [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 97 global ICSRs as of November 8, 2020 [3]. The reviewers have selected top quality cases with completeness score of 1.0 (28 ICSRs); among the reviewed cases, about half of them provides supportive association (7 probable, 1 possible association cases and 8 positive dechallenge).

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, considering the null value equal to zero. The results of (IC= 2.9) revealed a positive statistical association for the drug/ADR combination, which means "Hyperglycemia" and "Dolutegravir" have been observed noticeably more than expected when compared to other medications available in WHO database [3].

Literature review: In literature, multiple articles have been found supporting the association.

A case-report of African-American male living with HIV who switched to abacavir/lamivudine and dolutegravir after 16 years of treatment with abacavir/lamivudine and efavirenz. Approximately 3 weeks after the switch from efavirenz to dolutegravir, the patient presented to the emergency department with polyuria, polydipsia and visual changes. The results of initial evaluations showed that the patient had developed hyperglycemia. His medical history included DM type II. The patient self-discontinued dolutegravir and his self-reported blood glucose measurements improved [5].

Another article just published recently in 2020 describes this adverse drug reaction following the use of dolutegravir. The study presented some patients developed symptomatic hyperglycemia following transition to dolutegravir at the Infectious Diseases Institute Urgent Care facility. The authors concluded an association between hyperglycemia and dolutegravir initiation have been noticed and describes a clinical phenotype at risk for severe hyperglycemia. If patients with a long history of ART are to be switched to a dolutegravir-containing regimen, a monitoring plan for hyperglycemia should be part of the clinical care package [6].

Supportive Evidences

Class Effect: Evidence on class effect have also been mentioned in the literature. A reported case of 44-year-old male with a history of hemophilia A who developed diabetes mellitus four months after switching from abacavir, lamivudine, and efavirenz to abacavir, lamivudine, and raltegravir. Hemoglobin A1C normalized without further need for exogenous insulin after raltegravir was switched back to efavirenz [7].

Another case report of 46-year-old man who had been treated for type 2 diabetes with diet and exercise. He contracted HIV infection two years earlier and received highly active antiretroviral therapy (HAART). Three months before the current admission, HAART was switched from a non-nucleic acid reverse transcriptase inhibitor (NNRTI) to an integrase strand transfer inhibitor (INSTI) raltegravir. He developed diabetic ketoacidosis and was admitted for treatment and the adverse event was associated with INSTI [8].

Pharmacological Plausibility: The mechanism for the integrase strand transfer inhibitor (INSTI) has been reported in literature. It is hypothesized that INSTI-induced hyperglycemia is due to chelation of magnesium, thereby inhibiting the release and signaling of insulin [7].

International Regulatory Authorities: The U.S. FDA and Health Canada have mentioned hyperglycemia as adverse drug reaction that reported from clinical trials [9], [10].

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 dolutegravir and the risk of hyperglycemia. Health regulators and health care professionals must be aware for the potential risk and shall 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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