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"

20-9-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Azithromycin and the Risk of Cyanosis

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

Introduction

Azithromycin bind to 23S rRNA of 50S ribosomal subunit and prevents protein synthesis by inhibiting the assembly of the 50S ribosomal subunit. It is indicated to treat wide variety of infections including community-acquired pneumonia and pelvic inflammatory disease caused by susceptible organisms, including Legionella pneumophila, in patients indicated for IV therapy [1]. Cyanosis presents as an unusual bluish cast or discoloration of the skin and mucous membranes that is usually noticed around the lips, mouth, palms of the hands, fingernails and soles of the feet mostly due to low oxygen level in the blood [2]. The aim of this review is to evaluate the risk of Cyanosis associated with the use of Azithromycin 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 Azithromycin and the risk of Cyanosis [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 220 global ICSRs as of February 2021 [3]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.6 and above (8 ICSRs); the value 1.0 indicated the highest score for best-written ICSRs. Among the reviewed cases, more than half of them provides supportive association (1 certain and 5 possible 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 results of (IC= 0.8) revealed a positive statistical association for the drug/ADR combination, which means "Cyanosis" with the use of "Azithromycin" have been observed more than expected when compared to other medications available in WHO database [3].

Literature Upon conducting a literature search, a case-report found describing multiple episodes of hypotension and cyanosis. A 64-year old male Caucasian ex-smoker with a 9-year history of severe interstitial lung disease (ILD) presented with dyspnea and severe community-acquired pneumonia. He was prescribed daily IV azithromycin of 500 mg and IV ceftriaxone of 1 g and was admitted to the hospital. Each time when the patient get administered azithromycin infusion, he got severely hypotensive and cyanosis observed but get resolved immediately upon discontinuation of infusion [5].

Conclusion

The weighted cumulative evidences identified from the reported cases, data mining and literature are sufficient to support a causal association between Azithromycin and the risk of Cyanosis. 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. Pharmacia Upjohn Company LLC. Saudi Summary of Product Characteristics (SPC) of Azithromycin (ZITHROMAX) ®; (retrieved from EURS). [Accessed 2/4/2021]
2. Narayana health, Cyanosis. Available at: https://www.narayanahealth.org/cyanosis/ [Accessed on: 2/7/2021].
3. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org [Accessed 10/4/2020].
4. Uppsala Monitoring Center (UMC) (2020), 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 23/7/2020].
5. Hypotensive episodes associated with azithromycin infusion: a potentially fatal adverse drug reaction, Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6682541/ [Accessed 2/7/2021].