

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”

2-5-2021

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

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

Introduction

Azithromycin is antibiotic that indicated to treat community-acquired pneumonia and pelvic inflammatory disease caused by susceptible organisms, including Legionella pneumophila, in patients indicated for IV therapy ^[1]. Myocarditis is an inflammation of the heart muscle known as the myocardium which is the muscular layer of the heart wall ^[2]. The aim of this review is to evaluate the risk of Myocarditis 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 Myocarditis ^[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 16 global ICSRs as of February 1st 2021 ^[3]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.5 and above (7 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, 1 probable, and 2 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, considering the null value equal to zero. The results of (IC= - 0.4) revealed a negative statistical association for the drug/ADR combination, which means “Myocarditis ” with the use of “azithromycin” have been observed less than expected when compared to other medications available in WHO database ^[3].

Literature Upon conducting a literature search, multiple evidences were found.

A case report of a 48-year-old man presented with an upper respiratory tract infection and was prescribed a course of azithromycin. Within hours of the first dose, the patient developed fever and a diffuse maculopapular rash. He was given oral antihistamines and a 1-week prednisone taper. After he completed steroid course, the patient redeveloped fever, rash, fatigue and pruritus. Later he was diagnosed with Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) which was confirmed with skin biopsy. Two months later the patient experienced symptoms of myocarditis including (exertional dyspnea and pleuritic chest pain). Laboratory assessment revealed clinically significant finding including: elevated troponin I level of 5.96 ng/mL, leukocyte count, and a mildly elevated aminotransferase level. Electrocardiography showed sinus tachycardia with a right bundle-branch block pattern. The patient diagnosed with Hypersensitivity Myocarditis ^[5].

Another study aimed to detect signals of cardiac disorders associated with azithromycin from Health Canada database. The authors found that, myocarditis was reported in 5 out of 439 (1%) of the adult population among of all cardiac related ADRs ^[6].

Conclusion

The weighted cumulative evidences identified from the reported cases and literature are sufficient to support a causal association between Azithromycin and the risk of Myocarditis. 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. Health line. Available at: https://www.healthline.com/health/heart-disease/myocarditis#TOC_TITLE_HDR_1 [Accessed on: 2/10/2021].
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. Pursnani, A., Yee, H., Slater, W., & Sarswat, N. (2009). Hypersensitivity myocarditis associated with azithromycin exposure. *Annals of internal medicine*, 150(3), 225-226. [Accessed 2/8/2021].
6. International Journal of Pharmacy and Pharmaceutical Sciences. Available at: https://www.researchgate.net/publication/317366190_SAFETY_SIGNAL_DETECTION_OF_CARDIAC_DISORDERS_ADVERSE_DRUG_EVENTS_FOR_AZITHROMYCIN_IN_PEDIATRIC_POPULATION_USING_HEALTH_CANADA_ADVERSE_EVENT_REPORTING_SYSTEM_DATABASE [Accessed 2/8/2021].