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"

7-9-2020

Saudi Food and Drug Authority (SFDA) – Safety Signal of Skin Cancer Associated with the Use of Methotrexate products

*The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of **skin cancer** associated with the use of **methotrexate**. The signal has been originated as a result of routine medical literature monitoring as a pharmacovigilance activity.*

Introduction: Methotrexate (MTX) is an antimetabolite used to treat multiple conditions including neoplastic diseases, severe psoriasis, and rheumatoid arthritis. The exact mechanism of action still undiscovered however, MTX might affect immune function.[1] Skin cancer is the out-of-control growth of abnormal cells in the epidermis, the outermost skin layer, caused by unrepaired DNA damage that triggers mutations. These mutations lead the skin cells to multiply rapidly and form malignant tumors.[2]

Methodology: On July 2020, the Signal Detection team at Saudi Food and Drug Authority (SFDA) performed a safety review using National Pharmacovigilance Center (NPC) database as well as the World Health Organization (WHO) VigiBase, alongside with literature screening to retrieve related information for assessing the causality between skin cancer and methotrexate.

Results:

Literature: In literature, multiple articles have been found supporting the association of this signal, a recent randomized control trial published in 2020 revealed significant increase in skin cancer among MTX users.[3] Another study mentioned methotrexate increases the risk of non-melanoma skin cancer when used in combination with of immunosuppressant and biologic agents.[4] In addition, the incidence of melanoma for methotrexate users was 3-fold more than general population in a cohort study of rheumatoid arthritis patients.[5] Finally, Polesie, S., et

al. estimated the risk of cutaneous malignant melanoma (CMM) in a cohort study shows statistically significant risk increase for CMM was observed in MTX exposed patients.[6]

Cases review: Although there were no locally reported cases up to date, The WHO database (VigiBase) searched for individual case safety reports (ICSRs) reported for "Skin Cancer" and "Methotrexate" use, which yielded 121 ICSRs. Initial review revealed that 106 cases are insufficiently documented for proper medical assessment. However, the remaining fifteen cases have been assessed. As a result, 30 percent of the cases showed that MTX could possibly cause skin cancer, while five cases provides unlikely association and five un-assessable due to lack of information.[7]

Disproportionality analysis: The data mining 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 Uppsala Monitoring Centre to measure the reporting ratio. Results showed that combination of "Methotrexate" and "Skin cancer" observed more than expected when compared to other medications in WHO database (IC value is 1.2).[7]

Conclusion: The weighted cumulative evidences identified from global cases, data mining and published literature are sufficient to support a causal association between skin cancer and methotrexate. Therefore, health care professionals should be aware of this safety concern and may consider monitoring any signs or symptoms of skin cancer in patients treated with methotrexate.

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. DailyMed (2020), Methotrexate Drug Label Information; Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ec476b11-0b3c-4139-b1eb-a3daa76bc271 [Accessed 6/6/2020].
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3. Solomon, D. H., Glynn, R. J., Karlson, E. W., Lu, F., Corrigan, C., Colls, J., ... & Dellaripa, P. F. (2020). Adverse Effects of Low-Dose Methotrexate: A Randomized Trial. Annals of Internal Medicine, 172(6), 369-380.
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5. Buchbinder, R., Barber, M., Heuzenroeder, L., Wluka, A. E., Giles, G., Hall, S., ... & Ryan, P. F. (2008). Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Care & Research: Official Journal of the American College of Rheumatology, 59(6), 794-799.
6. Polesie, S., Gillstedt, M., Sönnergren, H. H., Osmancevic, A., & Paoli, J. (2017). Methotrexate treatment and risk for cutaneous malignant melanoma: a retrospective comparative registry-based cohort study. British Journal of Dermatology, 176(6), 1492-1499
7. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org [Accessed 6/6/2020].