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Methotrexate Associated Skin Cancer: A Signal Review of Pharmacovigilance Center

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Abstract : Introduction: Methotrexate (MTX) is an antimetabolite used to treat multiple conditions, including neoplastic diseases, severe psoriasis, and rheumatoid arthritis. 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. The aim of this review is to evaluate the risk of skin cancer associated with the use of methotrexate and to suggest regulatory recommendations if required. Methodology: 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. The search conducted in July 2020. Results: Four published articles support the association seen while searching in literature, a recent randomized control trial published in 2020 revealed a statistically significant increase in skin cancer among MTX users. Another study mentioned methotrexate increases the risk of non-melanoma skin cancer when used in combination with immunosuppressant and biologic agents. In addition, the incidence of melanoma for methotrexate users was 3-fold more than the general population in a cohort study of rheumatoid arthritis patients. The last article estimated the risk of cutaneous malignant melanoma (CMM) in a cohort study shows a statistically significant risk increase for CMM was observed in MTX exposed patients. The WHO database (VigiBase) searched for individual case safety reports (ICSRs) reported for “Skin Cancer” and 'Methotrexate' use, which yielded 121 ICSRs. The initial review revealed that 106 cases are insufficiently documented for proper medical assessment. However, the remaining fifteen cases have extensively evaluated by applying the WHO criteria of causality assessment. As a result, 30 percent of the cases showed that MTX could possibly cause skin cancer; five cases provide unlikely association and five un-assessable cases due to lack of information. The Saudi NPC database searched to retrieve any reported cases for the combined terms methotrexate/skin cancer; however, no local cases reported up to date. 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 the WHO Uppsala Monitoring Centre to measure the reporting ratio. Positive IC reflects higher statistical association, while negative values translated as a less statistical association, considering the null value equal to zero. Results showed that a combination of 'Methotrexate' and 'Skin cancer' observed more than expected when compared to other medications in the WHO database (IC value is 1.2). Conclusion: The weighted cumulative pieces of evidence identified from global cases, data mining, and published literature are sufficient to support a causal association between the risk of skin cancer and methotrexate. Therefore, health care professionals should be aware of this possible risk and may consider monitoring any signs or symptoms of skin cancer in patients treated with methotrexate.

Keywords : methotrexate, skin cancer, signal detection, pharmacovigilance
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