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Ibrutinib and the Potential Risk of Cardiac Failure: A Review of Pharmacovigilance Data

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Abstract : Introduction: Ibrutinib is a selective, potent, and irreversible small-molecule inhibitor of Bruton's tyrosine kinase (BTK). It forms a covalent bond with a cysteine residue (CYS-481) at the active site of Btk, leading to inhibition of Btk enzymatic activity. The drug is indicated to treat certain type of cancers such as mantle cell lymphoma (MCL), chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia (WM). Cardiac failure is a condition referred to inability of heart muscle to pump adequate blood to human body organs. There are multiple types of cardiac failure including left and right-sided heart failure, systolic and diastolic heart failures. The aim of this review is to evaluate the risk of cardiac failure associated with the use of ibrutinib 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 cardiac failure and ibrutinib. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases. Results: Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 212 global ICSRs as of July 2020. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.9 and above (35 ICSRs); the value 1.0 presents the highest score for best-written ICSRs. Among the reviewed cases, more than half of them provides supportive association (four probable and 15 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=1.5) revealed a positive statistical association for the drug/ADR combination, which means “Ibrutinib” with “Cardiac Failure” have been observed more than expected when compared to other medications available in WHO database. Conclusion: Health regulators and health care professionals must be aware for the potential risk of cardiac failure associated with ibrutinib and the monitoring of any signs or symptoms in treated patients is essential. The weighted cumulative evidences identified from causality assessment of the reported cases and data mining are sufficient to support a causal association between ibrutinib and cardiac failure.

Keywords : cardiac failure, drug safety, ibrutinib, pharmacovigilance, signal detection
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