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"

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Saudi Food and Drug Authority (SFDA) – Safety Signal of Rituximab and the Risk of Increased Aspartate Aminotransferase (AST)

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

Introduction

Rituximab is a chimeric mouse/human monoclonal antibody that indicated primarily for treatment of Non-Hodgkin's lymphoma (NHL) [1]. Rituximab cell destruction activity is mediated via binding to surface antigen CD20. Binding to CD20 induce direct signaling of apoptosis, complement activation and cell-mediated cytotoxicity [2]. Aspartate aminotransferase (AST) is a transaminase enzyme that catalyzes the conversion of aspartate and alpha-ketoglutarate to oxaloacetate and glutamate. It is found mostly in the liver, but it is present in muscles also. When the liver is damaged, it releases AST into the bloodstream [3]. The aim of this review is to evaluate the risk of Increased AST associated with the use of Rituximab 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 Rituximab and the risk of Increased AST [4]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [5].

Results

Case Review: As of September, 2021, there were 255 global Individual case safety reports (ICSRs) for the combined drug/adverse drug reaction [4]. Reviewers looked for causality in high-quality reported cases (cases with completeness score > 0.8, n=23). Six of the assessable ICSRs were in favor of

association, with one certain, two probable, and three possible. Furthermore, one case had a positive rechallenge, and four cases had a positive dechallenge [5].

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= 0.2) revealed a positive statistical association for the drug/ADR combination, meaning "Increased AST" with the use of "Rituximab" has been observed more than expected compared to other medications available in WHO database [4].

Literature: A 50-year-old woman with chronic lymphocytic leukemia (CLL) was treated with two cycles of rituximab/fludarabine/cyclophosphamide (R-FC). Her workup was within normal limits while she was in clinic for her fifth cycle, so she was given Rituximab 375 mg/m2 (total dose: 600 mg/d) on day one. Her hepatic enzymes spiked after 24 hours. The patient's history of other medical conditions was negative, and she did not report regular medication use. The administration of the scheduled subsequent chemotherapeutics (FC) according to the treatment protocol was postponed. Hepatobiliary ultrasonography, screening for hepatitis A, B, and C, as well as other infectious serologies such as Epstein- Barr virus, cytomegalovirus, human immunodeficiency virus, toxoplasma gondii, rubella, herpes zoster, and herpes simplex, and autoimmune serologies such as antiliver kidney microsome, anti-smooth muscle antibody, and anti-nuclear antibody were performed and were all negative. Following that, the patient was referred to the gastroenterology department for consultation [6].

Conclusion

The weighted cumulative evidence from reported cases, data mining, and literature is sufficient to support a causal association between Rituximab and increased AST risk. Health regulators and health-care professionals should be aware of this potential risk, and any signs or symptoms in treated patients should be closely monitored.

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:

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