SHORT COMMUNICATION

Hypokalemia Associated with Rituximab Use: Adverse Events- Signal Review

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Background: : Rituximab is an antineoplastic agent. It is a humanized chimeric CD20 directed monoclonal antibody. Hypokalemia is defined as a serum potassium level of less than (3.5 mmol/L). Saudi Food and Drug authority (SFDA) has detected a signal of Rituximab and hypokalemia from the Saudi National Pharmacovigilance database (NPC) and conducted this safety review based on that.

Objective: The purpose of this review is to evaluate the risk of hypokalemia in association with Rituximab use.

Methods: Signal Detection team at SFDA has conducted a retrospective search in the World Health Organization (WHO) database (Vigibase) and NPC database to retrieve all reported cases. Furthermore, literature screening was done for eligible publications.

Results: Local Cases:The search in (NPC) database resulted in three cases. By applying WHO causality assessment, all of the cases were unassessable.

Global Cases: On April 2th 2020, a search (WHO) database was conducted to retrieve all reported cases of Rituximab and Hypokalaemia between 2000 and 2020 via signal detection tool (Vigilyze). The search resulted in 250 Individualized Case Safety Reports (ICSRs). Almost half of cases concern female patients (47.3%). (26.7%) of ICSRs concern male patients while (26%) with unknown patient sex. A causality assessments was applied on serious cases with completeness score (>.83) (N=31). Resulted in two cases with probable association, eighteen cases with unlikely association, six cases with possible association and five unassessable cases.

One ICSR reported fatal outcome. Nine ICSRs reported positive dechallenge and two ICSRs reported positive rechallenge. Data mining: The disproportionality between a drug and event was measured using Information Component (IC) value that developed by WHO Uppsala Monitoring Centre. A Positive cumulative value (IC = 0.3) for spontaneous reporting suggests that the reported cases of Rituximab and hypokalaemia have been observed more than expected when compared to other medications in the WHO database. Literature: one eligible publication was found, a published phase 2 study was conducted to assess efficacy and toxicity of Temsirolimus and Rituximab combination in patients with relapsed or refractory mantle cell lymphoma. Hypokalaemia occurred in more than 10% of patients treated with rituximab.

Conclusion: The causality assessment resulted in eighteen cases with an unlikely association however, that is probably because the drug is usually administered with other antineoplastic medications that could cause hypokalemia.

Data mining resulted in positive IC value (0.3), which provided a potential statistical association between the drug and event. Moreover,The published phase two study make the association stronger. This safety review suggest that the current available evidence support a possible association between Rituximab and hypokalemia.

REFERENCES

1. DiMasi JA, Grabowski HG. Economics of new oncology drug development. *J Clin Oncol.* 2007;**25**:209–216. doi: 10.1200/JCO.2006.09.0803.
2. Aggarwal S. Targeted cancer therapies. *Nat Rev Drug Discov*. 2010;**9**:427–428. doi: 10.1038/nrd3186.
3. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, Filippini G, Skoetz N, Francis D, Lopes LC, Guyatt GH, Schmitt J, La Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Lunn MP, Tugwell P, Buchbinder R. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev*. 2011. p. CD008794.
4. Ghielmini M, Rufibach K, Salles G, Leoncini-Franscini L, Léger-Falandry C, Cogliatti S, Fey M, Martinelli G, Stahel R, Lohri A, Ketterer N, Wernli M, Cerny T, Schmitz SF. Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK) *Ann Oncol.* 2005;**16**:1675–1682. doi: 10.1093/annonc/mdi320.
5. Van Allen EM, Miyake T, Gunn N, Behler CM, Kohlwes J. Off-label use of rituximab in a multipayer insurance system. *J Oncol Pract.* 2011;**7**:76–79. doi: 10.1200/JOP.2010.000042.

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