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 Mycophenolic Acid and the Risk of Posterior Reversible Encephalopathy Syndrome (PRES)

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

Introduction

Mycophenolic Acid is classified as a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). The drug is an immunosuppressant combined with drugs such as Cyclosporine and corticosteroids to prevent organ rejection after hepatic, renal, and cardiac transplants [1]. Posterior reversible encephalopathy syndrome (PRES) presents with rapid onset of symptoms including headache, seizures, altered consciousness, and visual disturbance and may accompany acute hypertension. PRES is becoming more widely recognized, with a broad clinical spectrum of symptoms and triggers, but it is still poorly understood. A trigger is usually identifiable—most commonly, acute hypertension—but patients often have other comorbidities that may predispose them to PRES [2]. The aim of this review is to evaluate the risk of PRES associated with the use of Mycophenolic Acid 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 Mycophenolic Acid and the risk of PRES [3]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: There were 198 individual case safety reports (ICSRs) for the combined drug/adverse drug reaction as of April 2022 [3]. Applying the WHO causality assessment tool on 18 cases with completeness score (0.7) and above, revealed 5 PRES cases possibly related to Mycophenolic Acid [4].

Data Mining: Information component (IC), a tool developed by WHO-UMC to measure the reporting ratio, is used to estimate the disproportionality of the observed and expected reporting rates for drug/adverse drug reaction pairs. Positive IC values indicate a positive statistical association, whereas negative values indicate no statistical association. The results of (IC= 4.5) revealed that the drug/ADR combination has a positive statistical association. In other words, PRES has been observed more than expected with Mycophenolic Acid compared to other medications in the database [3].

Literature: the risk of PRES in association with Mycophenolic Acid was highlighted in the literature:

A 29-year-old female patient presented to hospital with a witnessed 3-minute seizure involving bowel incontinence, altered mental status, and tongue biting. The patient was started 4 days earlier on mycophenolic acid (dose available in full text article, full text article in not accessible). Magnetic resonance imaging of the head revealed bilateral posterior hemispheric subcortical edema, and the diagnosis of posterior reversible encephalopathy syndrome was made. Mycophenolate was immediately discontinued and replaced with cyclophosphamide [5].

A 22-year-old female prescribed Mycophenolic acid 500 mg twice daily for lupus nephritis. After 5 days, the patient developed sudden onset of headache, nausea, vomiting, followed by a witnessed 3-minute seizure involving altered mental status. Cerebrospinal fluid (CSF) was normal (Glucose: 55 mg/dL, protein (total): 20 mg/dL, gram stain: negative, culture: sterile). MARI of the brain was done 7 hours after the onset of headache and showed abnormal signal intensity involving parietal and occipital regions in T2 weighted, DWI, ADC and FLAIR, consistent with the diagnosis of PRES. A brain MRI 12 days after demonstrated resolution of the initial cerebral lesions [6].

Conclusion

The weighted cumulative evidence identified from the reported cases, data mining and literature are sufficient to support a causal association between Mycophenolic Acid and the risk of PRES. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

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. Allison, A. C., & Eugui, E. M. (2005). Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. Transplantation, 80(2 Suppl), S181–S190. https://doi.org/10.1097/01.tp.0000186390.10150.66
2. Roth, C., & Ferbert, A. (2011). The posterior reversible encephalopathy syndrome: what's certain, what's new?. Practical neurology, 11(3), 136–144. https://doi.org/10.1136/practneurol-2011-000010
3. Vigilyze.who-umc.org. 2022. [online] Available at: <https://vigilyze.who-umc.org/>
4. Uppsala Monitoring Center (UMC) (2022), The use of the WHO-UMC system for standardized case causality assessment; Available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1
5. Khajuria, B., Khajuria, M., & Agrawal, Y. (2016). Mycophenolate-Induced Posterior Reversible Encephalopathy Syndrome. American journal of therapeutics, 23(4), e1072–e1073. https://doi.org/10.1097/MJT.0000000000000270
6. Zhang, L., & Xu, J. (2018). Posterior reversible encephalopathy syndrome (PRES) attributed to mycophenolate mofetil during the management of SLE: a case report and review. American journal of clinical and experimental immunology, 7(1), 1–7.