

## 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”*

10-09-2024

### Saudi Food and Drug Authority (SFDA) – Safety Signal of Tacrolimus and the Risk of Hepatocellular carcinoma

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

#### Introduction

Tacrolimus is a medication used in the prevention and treatment of solid-organ transplant rejection. It is in the calcineurin-inhibitor class of medications. <sup>[1]</sup> Hepatocellular carcinoma (HCC) is a primary tumor of the liver and constitutes more than 90% of the primary tumor of the liver. Hepatocellular carcinoma occurs in approximately 85% of patients diagnosed with cirrhosis. HCC is now the fifth most common cause of cancer worldwide. <sup>[2]</sup> The aim of this review is to evaluate the risk of Hepatocellular carcinoma associated with the use of Tacrolimus and to suggest regulatory recommendations if required.

#### Methodology

Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between Hepatocellular carcinoma and Tacrolimus use. The search conducted on July 2024.

#### Results

**Case Review:** Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs). The WHO database resulted in 120 global case-reports while only one local case found. The authors used signal detection tool (Vigilyze) to retrieve all reported global cases. <sup>[3]</sup> Authors also applied WHO-UMC causality assessment criteria on the extracted ICSRs with completeness score 0.81 and above (n=29). <sup>[4]</sup> Among them, 3 cases were possibly linked to Tacrolimus, and 22 cases assessed as not assessable due to lack of valuable information, while the remaining 4 cases assessed as unlikely.

**Datamining:** 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 IC result is (3.5) for this drug/ADR combination which reflects strong positive statistical association. <sup>[4]</sup>

**Literature:** The signal team searched the literature to find related publications linking this ADR to Pembrolizumab. A study was done to elucidate the effect of tacrolimus treatment on tumor growth and metastasis of hepatocellular carcinoma (HCC). The authors concluded that tacrolimus enhanced the invasive potential of HCC cells, facilitating HCC lymphangiogenesis and promoting lymphatic metastasis in a rat model of HCC. <sup>[5]</sup>

### Conclusion

The weighted cumulative evidence identified from assessed cases, literature and disproportionality analysis are suggestive for causal association between Tacrolimus and Hepatocellular carcinoma. Health care professionals and health regulators must be aware of the potential risk in drug recipients.

### 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@sfd.gov.sa](mailto:NPC.Drug@sfd.gov.sa)

### References:

1. Araya AA, Tasnif Y. Tacrolimus. [Updated 2023 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK544318/>
2. Asafo-Agyei KO, Samant H. Hepatocellular Carcinoma. [Updated 2023 Jun 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559177/> [Accessed: 08/07/2024].
3. Vigilyze.who-umc.org. 2024. [online] Available at: <https://vigilyze.who-umc.org/> [Accessed: 08/07/2024].
4. World Health Organization WHO (2013). WHO-UMC system for standardised case causality assessment. Available at <https://www.who.int/publications/m/item/WHO-causality-assessment> [Accessed: 09/07/2024].
5. Zhou, S., Tan, C., Dai, Z., Zhu, H., Xu, M., Zhou, Z., ... & Fan, J. (2011, September). Tacrolimus enhances the invasion potential of hepatocellular carcinoma cells and promotes lymphatic metastasis in a rat model of hepatocellular carcinoma: involvement of vascular endothelial growth factor-C. In Transplantation proceedings (Vol. 43, No. 7, pp. 2747-2754). Elsevier.