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Correspondence on 'Cardiovascular toxicities associated with bispecific T-cell engager therapy' by Sayed *et al*

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We read with great interest the research article by Sayed *et al*.[1] Although it is very useful to understand the utilization of the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) for cardiovascular toxicity associated with bispecific T-cell engagers (BTEs), there are significant questions regarding the following. This analysis used data from Q4 2014 (the first approval of the BTE product, blinatumomab) to Q3 2023 (the latest date available). The only BTE products (blinatumomab, teclistamab, mosunetuzumab, glofitamab, and epcoritamab) currently approved by the FDA for the treatment of hematologic malignancies were included in the study. A multivariate logistic regression model with cardiovascular adverse event (CVAE) as the dependent variable was used to evaluate the association between different (CVAEs) and BTE to generate adjusted reporting OR (aROR). Independent variables included the variable of interest (BTE use) and factors (eg, age, sex, disease status, anthracycline use, an interaction between age and each of disease status and sex, and an interaction between disease status and sex.) that could potentially confound the relationship due to their association with the use of BTE and CVAEs. The Council for International Organizations of Medical Sciences VIII (CIOMS VIII) also states that adjustments such as stratification should be considered if the adjustment for covariates (eg, sex, age, region, and time to disease onset) can improve the sensitivity and/or specificity of the statistical analysis.[2] Therefore, at first glance, this study design is acceptable. However, there are database-specific caveats when adjusting covariates obtained from FAERS, a spontaneous reporting system.

ARE THE CASES REGISTERED IN THE FAERS SUFFICIENTLY REPRESENTATIVE OF ALL PATIENTS TREATED WITH THE DRUG?

The drug-related adverse event (AE) reports registered in FAERS are not data from the US alone (US: 69.2%, UK: 3.5%, Canada: 3.4%, Japan: 3.0%, France: 2.9%, and Germany: 2.2%).[3] Nonetheless, the largest number of reports surveyed are from the USA (43.2%), Japan (10.4%), and France (6.2%), with the remaining reports (40.2%) coming from 52 countries.[1]

The FDA's accelerated approval program approved blinatumomab in December 2014. Meanwhile, its approval in Japan was in September 2018. Teclistamab was approved for medical use in the European Union (EU) in August 2022, and in the USA in October 2022. Mosunetuzumab was approved for medical use in the EU in June 2022, and in the USA in December 2022. Glofitamab was approved for medical use in Canada in March 2023, the USA in June 2023, and the EU in July 2023. Epcoritamab was approved for medical use in the USA in May 2023, and in the EU and Japan in September 2023. At this time, teclistamab, mosunetuzumab, and glofitamab are not approved in Japan.

Although the patient population registered in the spontaneous reporting systems such as the FAERS has information about AEs up to a certain point in time, it is not known what patient population it represents out of the population that has been administered a particular drug. In extreme cases, the information may be biased due to concentrated reporting from specific countries (or medical institutions). There is no guarantee that the spontaneously reported patients adequately represent all patients who received the drug.[4]

Furthermore, there is a lot of missing age and sex information in the registered reports in the FAERS.[5] Sex data are missing in about 13% of all

reports. The annual proportion of missing age data increased over time, from 21.9% in 2002 to 43.8% in 2018.[5] It is, of course, unclear how these missing data may be biased. Since the information registered in FAERS may be biased and the degree of bias cannot be adequately assessed, the significance of easily adjusting covariates is unclear.[4] It is difficult to remedy this problem completely. However, given the BTEs' approval status, the region and time of disease onset will also need to be adjusted, as suggested by CIOMS VIII.

Sayed *et al* also evaluated the time to onset of CVAEs (vs non-CVAEs). Statistical significance was assessed using the Wilcoxon two-sample test. However, as mentioned previously, the BTEs investigated in this study are already approved in the USA. However, some BTEs are not approved at this time in the countries that have registered AE reports to FAERS. The timing of approval for each BTE also varies from country to country. For example, Japan has the second-highest number of BTE-related reports, but several BTEs were not approved at the time this study was conducted. In this approval situation of BTEs, it is not easy to evaluate the timing of onset in the following two points.

MAY DRUGS WITH SIGNIFICANTLY DIFFERENT APPROVAL DATES BE AFFECTED BY DIFFERENT REPORTING BIASES?

The registered data in the spontaneous reporting systems such as the FAERS are subject to reporting bias[3 4]; (1) the Weber effect is noted, according to which there is a brief increase in AE reports immediately after a drug is marketed, but overall, these reports tend to decline over time. (2) The notoriety effect is the general rise in the number of AE reports on a certain topic. (3) The ripple effect is a reporting bias that also increases the reporting of drugs in the same class as the reported drug. That is, how reporting bias affects BTEs approved in 2014 and those approved more recently may be different, which is unknown. It is not correct to evaluate the timing of onset of BTEs with different affected reporting biases as drugs in the same class (BTE product).

IS EVALUATING BTES WITH DIFFERENT TIME PERIODS BETWEEN APPROVAL AND STUDY COMPLETION AS ONE BTE PRODUCT CORRECT?

We are well aware that their paper is not the only case in which data for the same class of drugs are evaluated together. However, it is essential to note that in such cases, the drug has been used for a sufficient period after its approval. Figure 3 in their article shows the time to CVAE onset compared with non-CVAE.[1] However, the time frames for blinatumomab, approved in December 2014, and BTEs, approved in 2023, can be tracked are very different. Figure 3 shows a graph allowing for approximately 1000 days of follow-up, but for the BTE approved in 2023, 1000 days of follow-up is impossible because the study ends in September 2023. As stated by the authors, it is likely that CVAE is not uniform among different BTE products.[1] Therefore, this study design would not be a valid evaluation of the BTE product.

The signal scores and information up to the date of onset obtained from the spontaneous reporting systems, such as the FAERS, give us information on the early detection of unknown AEs and their required observation periods. Their report is the first postmarketing pharmacovigilance analysis to define CVAEs associated with BTE and provides much insight to the reader. On the other hand, their paper has research limitations that are not described, as indicated in this letter, and caution should be exercised in interpreting their results.

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REFERENCES

1 Sayed A, Munir M, Ghazi SM, *et al*. Cardiovascular toxicities associated with bispecific T-cell engager therapy. *J Immunother Cancer* 2024;12.
2 CIOMS Working Group VIII. Practical aspects of signal detection in Pharmacovigilance. CIOMS; 2010.
3 Noguchi Y, Tachi T, Teramachi H. Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief Bioinform* 2021;22.
4 Urushihara H. Basic dos and don'ts in applying signal detection methods to spontaneous reporting systems databases. *Jpn J Drug Inform* 2019;21:135–41.
5 Noguchi Y, Yoshimura T. Detection algorithms for simple two-group comparisons using spontaneous reporting systems. *Drug Saf* 2024.