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Reply: [Post-marketing safety concerns with Lecanemab: a disproportionality analysis using the FDA adverse event reporting system]

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Abstract
In this article, we have carefully read the author's comments on our published article regarding the post-marketing safety concerns of lecanemab based on the Food and Drug Administration Adverse Event Reporting System (FAERS) database. Pharmacovigilance studies based on the disproportionality analysis through the case/non-case design are common, and the details of this method deserve attention. We acknowledged the author's perspectives on the term "signal of disproportionate reporting (SDR)", and make some explanations on the SDR results for pancreatic carcinoma and the deduplication methods.

We deeply appreciate the valuable comments from our readers and address the main concerns here. Thanks for forwarding the comments regarding our recent publication regarding the post-marketing safety concerns of lecanemab based on the Food and Drug Administration Adverse Event Reporting System (FAERS) database, we have read them with great attention. We truly appreciate the recognition of the article's innovation and clinical significance, and take the raised concerns seriously. We would like to make some explanations for the comments, including the term "signal of disproportionate reporting (SDR)", the SDR results for pancreatic carcinoma and the deduplication methods.

First, the author suggests that the term "SDR" should replace "signal" in our article, given the limitations of disproportionality analyses methods. We adopt this suggestion and acknowledge that "SDR" is different from "signal". SDR represents a probabilistic computation of reporting frequencies, indicating the ratio of observed to expected values, and quantifies the likelihood of reporting suspected adverse drug reactions (ADRs) to a database [1]. For the results of the disproportionality analysis in our article, the use of "SDR" is more accurate. Thanks for the careful peer review and professional suggestion to promote better research. As mentioned in our article, due to the inherent limitations of pharmacovigilance research, its findings should be approached with caution.

Second, we reviewed each case associated with the identified SDRs. As the author did in their article, evaluating each case indeed allows for a better characterization of additional important clinical features available in the FAERS database. We appreciate the author for this valuable supplement. Regarding the SDR of pancreatic carcinoma, we are trying to look into the

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biological mechanism of pancreatic carcinoma and conducting further research on it. We probed and validated the mechanisms using network pharmacology from a bioinformatics perspective. Specifically, we analyzed the interaction networks between lecanemab and ADRs-related biological targets. Both the overall network and subnetwork modules 1 and 2 showed enrichment in pancreatic carcinoma (Disease Ontology database) and the pancreatic carcinoma signaling pathway (KEGG database), along with entries related to inflammation, multiple tumors, immunity, infection, and neuroendocrine regulation. Our unpublished research findings suggested potential mechanisms linking lecanemab to pancreatic carcinoma. However, the SDR of pancreatic carcinoma identified in our study is not robust, as the results varied after applying different deduplication approaches. It should be cautious to interpret the SDR results from small sample sizes. The SDR of pancreatic carcinoma need to be further verified and updated.

Third, the FAERS database collects data through spontaneous reporting, which may result in duplicate and withdrawn/deleted reports [2]. However, the process of removing duplicates varies across different studies. We adopted the same deduplication procedure as many other studies, such as those by Nie et al. [3], Gastaldon et al. [4] and Omar et al. [5], following the related file by FARES database. It is explained in detail in page 11 of "ASC_NTS.DOC" file in ASCII packet downloaded in Q1 2004 and page 10 of "FAQS.PDF" file in ASCII packet downloaded in Q1 2019. (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html)

Specifically, we selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table and sorted the reports using CASEID, FDA_DT, and PRIMARYID. For reports with the same CASEID, we kept the report with the largest FDA_DT value. Similarly, for both CASEID and FDA_DT, we retained the report with the largest PRIMARYID value. Additionally, starting from the first quarter of 2019, the data package for each quarter included a deletion report list. After data deduplication, reports were eliminated based on the CASEID listed in the deletion report list.

It is worth noting that there are no quality criteria for the procedure of deduplication. This author further deduplicated the cases according to gender, age, weight, reporter country, suspected drugs, adverse events, and event date. This approach can also be adopted [2]. When analyzing the adverse event (AE) of pancreatic carcinoma, we both identified two controversial cases. Despite the same demographic information, we retained both cases based on additional ancillary information [6], such as different "PRIMARYID", "reporting quarters", "indi_pt" (indication of all prescriptions the patient used), "indi_drug_seq"(all prescriptions the patient used) and "outc_cod" (outcomes). It is still not entirely certain whether the two cases belong to the same patient. Our approach is driven by caution, aiming to identify potential SDRs that warrant clinical attention. The SDR of pancreatic carcinoma still warrants further exploration in a larger sample.

We elaborated on the limitation of disproportionality methods in our published article, including the potential influence of confounding, such as AEs caused by concomitant medications. We are well-aware that further research is needed in the future to address these issues more comprehensively. We really appreciate this constructive feedback. We will remain committed to advancing pharmacovigilance methodologies and welcome ongoing discussions to refine lecanemab's safety assessment.

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Author contributions
X.X. and K.W. contributed equally to this work. X.X. and K.W. drafted the manuscript. All authors (X.X., K.W., and X.D.) critically revised the manuscript for important intellectual content. X.D. supervised the study and provided overall guidance. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was not required as the study was conducted using de-identified publicly available data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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