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Long-term surveillance of the anti-amyloid monoclonal antibody lecanemab: rights and duties of pharmacovigilance

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Abstract

The anti-amyloid monoclonal antibody lecanemab received the US accelerated approval for mild cognitive impairment or mild dementia stage of Alzheimer disease in January 2023, which was converted into traditional approval in June 2023. However, its regulatory assessment in Europe is still ongoing, and the European Commission has asked the Committee for Medicinal Products for Human Use of the European Medicines Agency to consider an update on the safety of lecanemab. Thus, timely post-marketing real-life studies are essential to clarify its long-term safety profile and to establish relevant place in therapy. In this regard, a recent study by Xing et al., analyzed individual case safety reports (ICSRs) collected in the Food and Drug Administration Adverse Event Reporting System (FAERS), a consolidated pharmacovigilance archive. In this Matters Arising article, we highlighted important methodological aspects that should not be overlooked by clinicians who are not fully familiar with this kind of study (the so-called disproportionality analysis through the case/non-case design), thus supporting enhanced awareness of stakeholders on interpretation, limitations and opportunities of FAERS data. To this end, we focused on the unexpected signal of pancreatic carcinoma raised by Xing et al., attempted to replicate the statistical findings and also provided a descriptive inspection of ICSRs: these are current rights and duties of modern pharmacovigilance to ensure evidence-based decision making.

Keywords Lecanemab, Anti-amyloid monoclonal antibodies, Pharmacovigilance, Individual case safety reports, Disproportionality analysis, Case-by-case analysis

The recent study by Xing et al., evaluated the post-marketing safety profile of lecanemab by assessing individual case safety reports (ICSRs) collected in the Food and Drug Administration Adverse Event Reporting System (FAERS), a consolidated pharmacovigilance archive [1]. Lecanemab is an important step in Alzheimer's disease (AD) treatment, shifting focus from symptoms management to modifying the underlying disease process. Nevertheless, its adoption hinges on careful patient selection, as it is only approved for patients with mild cognitive impairment or mild dementia. Safety monitoring requires baseline and periodic magnetic resonance imaging scans to detect and manage Amyloid-Related Imaging Abnormalities (ARIA), a known common complication globally affecting 21.3% of patients (in the forms of edema/effusion or microhemorrhage/hemosiderosis) [2]. Thus, considering the controversial regulatory approval (especially in Europe), the expectations and current clinical position in early symptomatic phase of AD, real-world studies

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are essential to clarify its long-term safety profile and to establish its place in therapy.

We commend the authors for timely addressing this hot topic: they employed the so-called case/non-case study design and performed a disproportionality analysis, which revealed a higher-than-expected reporting of different adverse events (AEs), further classified based on their predictability. Three key findings also emerged from the descriptive analysis, including: (1) a noteworthy rapidly increasing trend in the number of reports during the first 18 months on the market; (2) a longer time-to-onset for serious AEs as compared to non-serious AEs; (3) a more frequent co-reported polypharmacy for AD, aspirin, acid-suppressing medications, statins, antidepressants or benzodiazepines in patients with serious AEs. Of note, these reporting features mirror the scenario recently observed for esketamine [3], thus further contributing to the need for urgent clarification on the benefit-risk profile of lecanemab.

We concur with the authors on the value of ICSRs databases as irreplaceable tools for timely real-life post-marketing surveillance. Nevertheless, we would like to highlight key issues that should not be overlooked by clinicians who are not fully familiar with this kind of study design.

First, the reporting odds ratio (ROR) and information component (IC), recognized disproportionality measures to detect potential drug-event associations, should not be interpreted as relative risk, since the so-called case/non-case design on ICSRs only mirrors the case-control study in pharmaco-epidemiology. Due to inherent limitations, including unpredictable directionality of biases (under-reporting and stimulated reporting), lack of denominator (population exposure) and inability to infer causality, a statistically significant disproportionality (even when two disproportionality measures consistently met pre-specified threshold criteria) cannot be automatically interpreted as a safety alert, but should rather be referred to as the so-called "signal of disproportionate reporting" (SDR), simply indicating a higher-than-expected reporting [4].

Second, an SDR should be complemented by a case-by-case analysis, especially for unexpected, rare but serious AEs with delayed onset, such as cancer. This would allow to better characterize additional important clinical features available in FAERS, including dechallenge/rechallenge, co-reported events (possibly reflecting a more complex syndrome) and concomitant drugs (being proxies of comorbidities or acting as risk factors). A careful consideration of plausibility (biological, pharmacological and clinical) and a global evaluation of the evidence (including pre-clinical data, if available) are encouraged to prioritize the need for subsequent analytical pharmaco-epidemiological approaches such as cohort studies. A researcher may ask the so-called *Freedom Of Information Act*, namely the access to narratives, potentially including additional clinical data that can be useful for causality assessment.

Special attention should be given to the 4 cases of pancreatic carcinoma (with relevant SDR) that have not been individually inspected by Xing et al., [1] with the exception of time-to-onset, which, surprisingly, largely exceeded the post-marketing 18-month period of the FAERS analysis (1170 days), thus suggesting that the patients started lecanemab during pre-marketing clinical trial phase. Moreover, the underlying mechanistic basis and plausibility remains elusive: based on the Food and Drug Administration assessment, pre-clinical carcinogenicity studies have not been conducted because of the lack of pharmacological activity in rodent species (mouse, rat), and the development of neutralizing anti-drug antibodies, thus making standard carcinogenicity studies unfeasible [5].

Third, transparency and accuracy are current mantras in modern pharmacovigilance, and the recent READUS-PV guideline supports researchers and other stakeholders in the reporting of a disproportionality analysis [6]. Remarkably, two pharmacovigilance studies investigating the safety of lecanemab *via* FAERS have been simultaneously published in different Journals [7, 8], thus raising the question on potential variability and actual reproducibility of results [9]. Notably, an SDR of pancreatic carcinoma was also detected by Li et al., [7] and this prompted us to replicate the analyses, especially because the FAERS archive has unique features, thus necessitating extensive data preprocessing and curation (e.g., duplicate removal, codification standardization and correction of drug names) [10, 11].

After deduplication (according to gender, age, weight, reporter country, suspected drugs, AEs, event date), 3 cases were extracted from FAERS (submission date to FDA between January 1, 2023 and June 30, 2024). We calculated ROR and IC with relevant 95% confidence interval (CI) as measures of disproportionality. No SDR was found for lecanemab and pancreatic carcinoma [ROR = 4.14 (95% CI = 0.85–12.17); IC = 1.51 (95% CI = -0.56-2.71). The results of the descriptive case-by-case inspection of cases are presented in Table 1. Thus, this question remains open to further investigation.

As a *final reflection*, the question arises on the true value of disproportionality analysis to detect drug-induced malignancies [12]. The main use of this method is to confirm (or not) a potential association based on a pharmacological hypothesis between a specific drug and an AE, thus supporting a suspected adverse drug reaction [13]. This can be illustrated by the relation between pioglitazone and bladder cancer [14]. In the context of a pharmacological hypothesis, the advantage of the

Table 1 Case-by-case evaluation

Patient	Gender; Age, in years	Reporter country	Co-reported events	Start date	Event date	Time to onset, in days	Co-reported drugs as potential confounders*	Co-reported drugs influencing gene transcription
#1	M; 79	Japan	None	2020-11-06	2023-03-17	862	sitagliptin, ipragliflozin	None
#2	F; 87	USA	jaundice	2019-08-05	2023-02-08	1284	None	raloxifene
#3	F; 74	Japan	femur fracture	2019-02-20	2022-08-11	1269	None	bazedoxifene

* Diabetes can increase the risk of cancer *per se* (the so-called cofounding by indication); ipragliflozin is a sodium-glucose cotransporter 2 inhibitor used in type 2 diabetes mellitus, whereas sitagliptin is a dipeptidyl peptidase-4 inhibitors, a pharmacological class that has been also potentially associated with pancreatitis and pancreatic carcinoma

disproportionality method is the speed of its implementation. Conversely, the application of disproportionality approaches to automatically generate SDRs (i.e., without *a priori* pharmacological hypothesis) in the regulatory context of recently approved drugs requiring stringent post-marketing surveillance is not always satisfactory if not guided by a clinical/pharmacological rationale [4, 13].

Although we strongly believe in the role of ICSRs databases to timely detect rare long-term safety issues, which cannot be captured or fully appreciated within clinical trials, in our opinion the unexpected SDR of pancreatic carcinoma identified by Xing et al., [1] cannot be qualified as a true safety alert. We were unable to reproduce disproportionality analysis and, most importantly, our case-by-case analysis identified only 3 cases originating from pre-marketing clinical trials, and revealed potential confounders. Therefore, the conduct of *ad hoc* analytical observational studies, taking advantage of the European Data Analysis and Real World Interrogation Network (https://www.ema.europa.eu/en/about-us/how-we-work/big-data/real-world-evidence/data-analysis-real-world-interrogation-network-darwin-eu) and the US Sentinel initiative (https://www.sentinelinitiative.org/), is not justified for now. We do support a targeted proactive surveillance of lecanemab and other anti-amyloid monoclonal antibodies both by clinicians and other pharmacovigilance stakeholders, considering drug utilization data as a complementary perspective of ICSRs. This will hopefully allow a global trustful pharmacovigilance assessment, supporting more evidence-based decision making. Of note, as of January 28th, 2025, the European Commission has asked the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency to consider information on the safety of lecanemab that became available after the adoption of the CHMP opinion in November 2024 and whether this may require an update of the opinion, including whether the wording of the risk minimization measures is clear enough to ensure correct implementation.

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None.

Author contributions
MD and AB had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; concept and design: MD, EP, ER; acquisition, analysis, or interpretation of data: all authors; drafting of the manuscript: DM, ER; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: MD, AB; supervision: ER.

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Data availability
The datasets generated and/or analyzed during the current study are publicly available in the FDA Adverse Event Reporting System (FAERS) database (https://fs.fda.gov/extensions/FPD-QDE-FAERS/FPDQDE-FAERS.html). The algorithm for cleaning FAERS data is open-source at https://github.com/fusarolimichele/DiAna, and the cleaned database is available on an OSF repository (https://osf.io/zqu89/) and through the R package DiAna [11]. The code generated and/or analyzed in the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval was not required since FAERS data are anonymous and publicly available.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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