The value of case reports and spontaneous reporting systems for pharmacovigilance and clinical practice

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The value of case reports and spontaneous reporting systems for pharmacovigilance and clinical practice

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We greatly appreciate a recent Editorial remarking the value of published case reports in drug safety and underlines the too often overlooked importance of reporting adverse drug reactions (i.e., adverse events suspectedly attributed to drug exposure) to a pharmacovigilance system. [1]

Dermatologists are facing new challenges in real-world pharmacovigilance. On one hand, skin manifestations are increasingly documented with anticancer drugs and require multidisciplinary management since cutaneous adverse events have been proposed as potential biomarkers of drug efficacy, implying a delicate balance between timely interruption of the offender (with medical treatment) and early resumption to avoid cancer recurrence or progression. A recent example includes immune checkpoint inhibitors, which may cause a variegate spectrum of skin toxicity, including rare but serious cutaneous adverse reactions, namely Stevens-Johnson syndrome, Toxic epidermal necrolysis, and Drug Rash with Eosinophilia and Systemic Symptoms. [2]

On the other hand, the widespread use of biologicals such as monoclonal antibodies in cutaneous diseases (e.g., psoriasis) requires new diagnostic skills to dermatologists, who should become aware of rare but potentially serious non-dermatological events such as infections, neuro-psychiatric and cardiovascular risks. In fact, these potentially innovative drugs are usually marketed through accelerated pathways, namely shortened review time and conditional approval, thus implying provisional evidence of efficacy and safety due to underpowered clinical trials and their inability to fully capture rare adverse events, strengthening the role of proactive pharmacovigilance monitoring. Examples include novel IL-17 (e.g., secukinumab, bradolumab), and IL-23 antagonists (e.g., ustekinumab, tildrakizumab), for which both acute and long-term unexpected concerns have been described (e.g., malignancies with ustekinumab). [3]

In this regard, pharmacovigilance databases represent an unprecedented opportunity not only to perform real-world post-marketing studies on biological medications in dermatology [4], but also to provide a real-time overview of major toxicities, thus informing clinical practice for proactive monitoring. Of note, these archives mainly contain unpublished case reports and can be queried through online tools by individual researchers (**Table 1**). This is the case of the FDA Adverse Event Reporting system (FAERS), which allows: 1) data visualization and download through a public dashboard (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard); 2) access to raw data for customized analyses), namely disproportionality algorithms aiming at detecting higher-than-expected reporting of a given adverse event; 3) access to individual cases (narratives) through a direct request to the FDA. Thus, these spontaneous reporting systems can add clinical and pharmacological substantiation to case reports by detecting a potential drug-event association, also known as “signal”. In line with case reports, firm causative role cannot be inferred, and

signals, even when statistically robust, warrant verification through dedicated prospective research or meta-analysis to support a real association.

Notwithstanding limitations, case reports individually published or collectively gathered in spontaneous reporting systems represent a valuable and irreplaceable opportunity for real-world assessment of post-marketing safety of medications.

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Table 1. Overview of major international spontaneous reporting databases that can be queried through publicly available online tools.

Database	Website	Time window	Products covered	Catchment area	Search criteria (customization)
FDA Adverse event Reporting System (FAERS)	https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard	1969 (2004 for data download)-present	Medicines *	Worldwide (20 million reports)	By medication (up to five)/reaction # Raw data can be also downloaded $
WHO-Vigibase	http://www.vigiaccess.org/	1968-present	Medicines and vaccines	Worldwide (over 110 Countries)	By product
Eudravigilance	http://www.adrreports.eu/en/index.html	2001-present	Medicines authorized in the European Union ±	Europe	By product/substance
Australian Database of Adverse Event Notifications (DAEN)	https://www.tga.gov.au/database-adverse-event-notifications-daen	1971-present	Medicines and vaccines licensed in Australia	Australia	By product, data range, organ/system/toxicity
Canada Vigilance Adverse Reaction Online Database	https://cvp-pcv.hc-sc.gc.ca/arq-rei/index-eng.jsp	1965-present	Medicines, vaccines and health products licensed in Canada	Canada	By product, date, seriousness, demographic information, ADR term

ADR: adverse drug reaction.

± Medicines approved through non-centralized procedure are also present.

* Devices, vaccines, and other products (e.g., food supplements) are not included, as they are specifically recorded in ad hoc databases: MAUDE—Manufacturer and User Facility Device Experience (ttps://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM), VAERS—Vaccines Adverse Event Reporting System (https://vaers.hhs.gov/data/datasets.html), and CAERS—Center for Food Safety and Applied Nutrition Adverse Event Reporting System (https://www.fda.gov/food/complianceenforcement/ucm494015.htm).

Customized analyses without data download are also possible through online systems, named AERSMine (https://research.cchmc.org/aers/home) and OpenVigil http://openvigil.pharmacology.uni-kiel.de/openvigilfda.php).

$ FAERS data can be extracted in different formats, namely download quarterly files (https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files), and APIs (https://open.fda.gov/).