Exploring the 'risk': Comments on the FAERS data regarding the safety of JAK inhibitors by Mikaeili *et al.*

Sirs,

I read with great interest the article by Mikaeili *et al*. on the safety profile of JAK inhibitors in rheumatoid arthritis using the FAERS database (1). The study evaluates tofacitinib, baricitinib and upadacitinib, comparing various adverse events using 'risk' assessments. However, I believe that clarifying certain aspects related to the study design, terminology, and the nature of the database would enhance the comprehensibility of the study.

Using the term 'risk' in epidemiology

In epidemiology, 'risk' refers to the probability or likelihood that an individual within a defined population will develop a specific disease or experience a particular health-related event over a given period (2). It is a fundamental measure for assessing disease occurrence and evaluating exposure-outcome relationships. Typically, randomised controlled trials (RCTs) and cohort studies allow for calculating absolute risk, attributable risk, and relative risk (3). Risk estimations are attempted for study designs outside these frameworks, but technically, using terms like 'risk' or 'risk factor' in such studies may lead to confusion. Although 'risk' does not directly imply causality, the temporal aspect of cohort and RCT designs allows them to infer causality more strongly than disproportionality analyses or other observational methods.

Furthermore, in a review by Cutroneo *et al*., which discusses the reporting of disproportionality analyses, it is explicitly recommended that disproportionality analysis results should not be presented in a way that implies drug-related risk or causality, nor should risk ranking be performed (4). Instead, it is advised that terms like 'safety signal' or 'disproportionate reporting' be used. Given the high exposure to confounding factors in spontaneous reporting data, presenting the findings using the term 'risk"'may amplify the perceived strength of the conclusions, potentially making spurious associations appear significant while causing true associations to be overlooked.

Potential bias in FAERS data reporting

The FAERS database allows reports submitted by healthcare professionals (physicians, pharmacists and other medical personnel) and patients or their caregivers (5). This dual reporting introduces an inherent source of bias, which may affect data interpretation. Stratifying the data based on the type of reporter would provide further insights and help control for potential biases introduced by patient-reported outcomes.

Interpretation of musculoskeletal symptoms as the most frequently reported adverse events

One of the most frequently reported adverse events in the study is musculoskeletal symptoms, which is quite unexpected given that RA patients take these medications primarily to alleviate joint inflammation and pain. This raises the question of whether the FAERS database structure allows a clear distinction between adverse drug reactions (ADRs) and disease-related symptoms. There is a strong possibility that some reports may confuse pre-existing RA symptoms with drug-induced adverse events. Consequently, such misclassification could significantly affect the validity of the analysis and the conclusions drawn. Addressing this potential overlap between disease symptoms and ADRs is crucial to ensuring the reliability of the study's findings.

I would like to thank the authors for their efforts and willingness to consider these comments as constructive criticism.

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References

1. MIKAEILI B, ALQAHTANI ZA, HINCAPIE AL, GUO JJ: Safety of Janus kinase inhibitors in rheumatoid arthritis: a disproportionality analysis using FAERS database from 2012 to 2022. *Clin Rheumatol* 2025; 44(4): 1467-74. https://doi.org/10.1007/s10067-025-07360-9
2. JEWELL NP: Risk comparisons. *Am J Ophthalmol* 2009; 148(4): 484-86. https://doi.org/10.1016/j.ajo.2009.06.020
3. WANG JJ, ATTIA J: Study Designs in Epidemiology and Levels of Evidence. *Am J Ophthalmol* 2010; 149(3): 367-70. https://doi.org/10.1016/j.ajo.2009.08.001
4. CUTRONEO PM, SARTORI D, TUCCORI M *et al*.: Conducting and interpreting disproportionality analyses derived from spontaneous reporting systems. *Front Drug Saf Regul* 2024; 3. https://doi.org/10.3389/fdsfr.2023.1323057
5. GOLDMAN A, GALPER BL, DRUYAN A *et al*.: Adverse cardiovascular events in rheumatoid arthritis patients treated with JAK inhibitors: An analysis of postmarketing spontaneous safety reports. *Semin Arthritis Rheum* 2024; 67: 152461. https://doi.org/10.1016/j.semarthrit.2024.152461