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CORRESPONDENCE ON

Correspondence on: "Real-world safety data of first-line drugs for rheumatoid arthritis: insights from the Portuguese Reuma.pt database"

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Dear Editor,

We read with great interest the study by Ramos Rodrigues et al. describing adverse event (AE) reports from the Portuguese Reuma.pt registry, representing the first comprehensive real-world safety analysis of first-line rheumatoid arthritis (RA) therapies in this population.[1,2] The authors report that among 1,880 AE entries, 377 (20.1%) were attributed to first-registered disease-modifying antirheumatic drugs (DMARDs), with methotrexate accounting for 62.9% of reports; notably, 46.7% led to treatment discontinuation despite 86.8% being classified as non-serious[1]. These data provide valuable national safety insights, but several methodological clarifications would materially strengthen interpretation and reduce the risk that clinicians over-infer comparative drug safety from event counts. We summarise the main requests in Table I.

Exposure denominators and unit of analysis (counts versus rates)

The analysis is presented primarily as counts of AE entries by drug[1]. Because treatment uptake varies substantially across first-registered therapies in routine care, raw AE counts cannot be interpreted as comparative risk without denominators. We therefore encourage presentation of (i) the number of patients exposed to each first-registered DMARD and, where feasible, (ii) exposure time (patient-years) to report incidence rates (e.g., per 100 patient-years). Given that Reuma.pt captures treatment initiation dates[2], such denominators appear feasible to extract. Reporting guidance for pharmacoepidemiology using routinely collected health data emphasises transparent definitions of exposure, outcome ascertainment and denominators to support reproducibility and valid inference[3,4]. In addition, it would be helpful to clarify whether multiple AE entries from the same patient were included and analysed as independent observations. A patient-level sensitivity analysis (e.g., first AE per patient) could reduce inflation from repeat reporters. The authors' clarification that AE entries, rather than unique patients, served as the unit of analysis further underscores the importance of patient-level sensitivity analyses in future Reuma.pt safety reports.

'First-line' in the registry versus 'first-line' in guidelines & clinical practice

In the methods, first-line therapies are defined as those "occurring under the drug registered as the patient's initial treatment in the Reuma.pt registry."[1] This operational definition is pragmatic for registry analyses but differs from how 'first-line RA therapy' is commonly understood in contemporary guidelines (true treatment initiation, typically methotrexate ± short-term glucocorticoids)[5,6]. A brief wording refinement (e.g., 'first-recorded DMARD in Reuma.pt') or stratification by disease duration at registry entry could prevent misinterpretation and improve cross-cohort comparability.

Seriousness/severity and causality: aligning registry fields with standard pharmacovigilance terminology

The study reports AE 'severity' using 'serious/non-serious' labels and provides causality categories ('probable/possible/definitive/unlikely')[1]. In pharmacovigilance, 'serious' has a specific regulatory meaning (e.g., death, life-threatening event, hospitalisation, disability), which is distinct from clinical 'severity.'[7] We suggest the authors clarify the operational definition used in Reuma.pt for 'serious' events and align it explicitly with standard criteria[7]. Similarly, if the causality fields were mapped to an established framework (such as the WHO-UMC system[8]), stating this would enhance transparency; if not, future registry iterations could consider standardising causality assessment using such frameworks to reduce variability inherent to clinical judgement-based categorisation.

Missingness, key covariates and confounding by indication

The authors appropriately acknowledge limitations, in-

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TABLE I. Minimum additional information/definitions to interpret first-registered DMARD AE counts as comparative safety signals in Reuma.pt

Domain	What is currently reported[1]	What to add/clarify	Why it matters
Exposure denominators	AE counts by drug	Number exposed to each first-registered DMARD; patient-years (if available)	Converts 'most frequent' into interpretable rates
Unit of analysis	AE entries	Multiple AEs per patient? Any clustering? Patient-level sensitivity (first AE per patient)	Avoids inflation from repeat reporters
'First-line' construct	First drug recorded in Reuma.pt	Wording refinement (first recorded DMARD); stratify by disease duration at registry entry	Prevents guideline-language confusion
Seriousness/severity	Serious/non-serious labels	Operational definition aligned to standard 'serious AE' criteria[7]	Reduces cross-study ambiguity
Causality	Probable/possible/definitive/unlikely	Specify framework used (e.g., WHO-UMC system[8]); standardised criteria	Improves reproducibility and inter-centre consistency
Missingness & confounders	Limited covariates: some fields are missing	Missingness summary: capture dose/route/folate, key comorbidities, concomitant meds	Strengthens clinical interpretability

AE: adverse event; DMARD: disease-modifying antirheumatic drug; WHO-UMC: World Health Organization – Uppsala Monitoring Centre.

cluding absent information on methotrexate dose and potential underreporting[1]. Several registry fields also have substantial missingness and causality assessment was unavailable in a proportion of reports[1]. A concise 'missingness by variable' summary would allow readers to judge the likelihood of selection bias and the robustness of sex/age associations[3,4].

Clinically, dose, route, folate supplementation, comorbidity burden and concomitant glucocorticoids/non-steroidal anti-inflammatory drugs are central confounders in AE attribution and discontinuation decisions. A minimal safety module capturing these items could markedly improve signal interpretability, particularly in older patients and other high-risk groups emphasised in treatment guidelines and their evidence base[5,6,9]. These clinical data were registered in Reuma.pt by trained rheumatologists[1], suggesting that structured collection of key safety covariates would be both feasible and valuable.

Additionally, the marked discrepancy between median treatment duration (1.27 years) and disease duration (8.56 years) at AE onset[1] suggests that many 'first-line' registry entries may represent delayed treatment initiation rather than contemporary treat-to-target practice[5,6], further complicating interpretation. The authors report significant sex-based differences in AE severity, with male patients experiencing twice the odds of severe events (OR = 2.31; 95% CI: 1.17–4.55)[1]. While biological mechanisms (immune regulation, pharmacokinetics, hormonal factors) may contribute, the absence of data on comorbidities and concomitant medications limits causal inference[10]. Recent evidence from inflammatory rheumatic disease cohorts suggests that sex differences in adverse drug reactions may be influenced by baseline disease severity, polypharmacy, and healthcare-seeking behaviour[10], factors that warrant explicit consideration in future Reuma.pt safety analyses.

Internal consistency of tabulated data

Finally, we noted potential discrepancies in tabulated data: specifically, the sex-stratified counts for 'prior similar reaction' in Table I do not appear to reconcile with the overall totals[1], and golimumab appears in Table II (drug-to-event interval) but is not explicitly listed among first-registered drugs in Table I[1]. We would appreciate clarification of the denominators used (total N versus valid non-missing cases) and whether rare drugs were intentionally excluded from frequency tabulations. Addressing these points would prevent inadvertent misinterpretation and further strengthen this valuable national safety snapshot.

CONCLUSION

In conclusion, this study provides an important real-world overview of AE reporting in RA within Reuma.pt and represents a significant contribution to Portuguese rheumatology pharmacovigilance[1,2]. Adding exposure denominators, clarifying the 'first-line' construct, and standardising seriousness and causality definitions would substantially enhance interpretability and facilitate meaningful comparisons across international registries, while remaining feasible within Reuma.pt's established data collection framework[2].

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