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LETTER

Letter to the Editor Regarding: "Cardiovascular and Kidney Outcomes After Systemic Treatment for Plaque Psoriasis: A Systematic Review and Network Meta-Analysis"

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To the Editor,

We read with interest the recent article by Shi et al., "Cardiovascular and Kidney Outcomes After Systemic Treatment for Plaque Psoriasis: A Systematic Review and Network Meta-analysis" [1]. The authors made a substantial effort to assess the comparative cardiovascular and renal safety of systemic therapies for psoriasis using network meta-analysis (NMA) methodology. While the overall intent of the study is commendable and the topic of clear clinical relevance, we are deeply concerned about the validity and implications of the cardiovascular safety results and their interpretation.

The primary limitation of the cardiovascular analysis lies in the extremely low number of events across included trials. Major adverse cardiovascular events (MACE) are rare in randomized controlled trials (RCTs) for psoriasis, which are typically short in duration and exclude patients with significant baseline cardiovascular risk. Consequently, the reported odds ratios for MACE and total cardiovascular events—particularly for comparisons such as ixekizumab vs. bimekizumab (OR 31.92; 95% CI 2.01–1123.25) and infliximab vs. ixekizumab (OR 64.77; 95% CI 1.61–9576.55)—are accompanied by extraordinarily wide confidence intervals that render the effect estimates highly unstable and statistically unreliable. While the authors acknowledge this to some extent, the discussion presents these findings with a level of certainty that is disproportionate to the fragility of the underlying data. Additionally, the suggestion that bimekizumab may offer cardiovascular protection is based on an odds ratio of 0.06 with a 95% confidence interval ranging from 0 to 0.80. A lower bound of zero for an odds ratio is mathematically invalid and typically reflects either zero events or model instability, thereby

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precluding any robust statistical inference. Such results must be considered exploratory and hypothesis-generating at best—not definitive evidence of cardioprotection.

The authors state they used a NMA within a Bayesian framework using random effects; this may be standard for response rates (there is no league table in the paper), but the model may not be appropriate for rare events. Standard random effects models within a Bayesian framework may be unsuitable for rare events because the normal approximations they rely on can be inaccurate, leading to biased effect estimates, especially when event counts are extremely low or zero in some study arms. For rare event meta-analyses, it is crucial to predefine the analysis approach, avoid continuity corrections, and conduct sensitivity analyses to ensure robustness [2–4].

Moreover, the paper states that "no head-to-head clinical trials have been conducted," which is inaccurate—several head-to-head RCTs comparing systemic agents in psoriasis do exist and appear to be included in the NMA.

Similarly, the choice of Week 24 as common timepoint for all outcomes, including safety, does not correspond to the standard placebo-controlled duration of most psoriasis trials, which often ends at Week 12 or 16. This discrepancy may introduce inconsistencies in effect estimation across trials.

An equally important limitation—largely unaddressed in the manuscript—is the lack of adjustment for baseline cardiovascular risk or other relevant confounding variables. The populations enrolled across the included trials were heterogeneous, and what is often overlooked is that the baseline cardiovascular risk may have differed substantially between treatment arms and across studies. Many trials excluded individuals with known cardiovascular comorbidities or enrolled populations with differing age, sex distribution, smoking status, obesity rates, and prior treatment exposure. Yet, no subgroup analyses were conducted to stratify results by these important factors, nor were network meta-regressions applied to mitigate between-study variability. As a result, any observed differences in cardiovascular outcomes may simply reflect underlying population characteristics rather than true differences in treatment-related risk. In the absence of individual participant data and appropriate confounder adjustment, the validity and interpretability of the comparative cardiovascular safety estimates remain fundamentally limited.

Despite these limitations, the manuscript asserts that ixekizumab may increase cardiovascular risk and suggests that ustekinumab may also be of concern. These interpretations are not only based on weak data but are presented with terminology that lacks biological accuracy. The use of the term "cardiotoxicity" to describe ixekizumab is particularly problematic. "Cardiotoxicity" implies direct myocardial injury, typically seen with agents such as anthracyclines or tyrosine kinase inhibitors. There is no preclinical, clinical, or pharmacovigilance evidence supporting such an effect for IL-17A inhibition. Using this term in the context of immunomodulatory therapies is inappropriate and may lead to misinterpretation by clinicians and patients alike.

Furthermore, the discussion advances a speculative mechanistic rationale in which dual inhibition of IL-17A and IL-17F (as with bimekizumab) is hypothesized to be cardioprotective, whereas selective IL-17A inhibition (as with ixekizumab and secukinumab) is portrayed as potentially harmful. This narrative is both selective and scientifically unfounded. IL-17A is well established as a pro-atherogenic cytokine, implicated in vascular inflammation and plaque instability [5]. The claim that IL-17F is more relevant to cardiovascular pathology lacks convincing experimental or translational support. Moreover, the observed increase in cardiovascular events with sonelokimab—another IL-17A/IL-17F inhibitor—directly contradicts the authors' proposed mechanism.

Most importantly, the authors do not reconcile their findings with the extensive real-world data that overwhelmingly refute these associations. Long-term extension studies and registry-based data have consistently demonstrated a low incidence of MACE across all major biologic classes, including IL-17 inhibitors and ustekinumab [6–8]. Additionally, both ustekinumab and IL-17A inhibitors have been associated with improvements and favorable modulation

of cardiovascular biomarkers [9, 10]. The early concern regarding ustekinumab and cardiovascular events has long been addressed by robust observational and mechanistic studies, which consistently report neutral or beneficial effects.

Given the methodological limitations described above, we are concerned that the strength of the authors' conclusions and the language used may mislead readers, create unnecessary alarm, and potentially undermine treatment confidence. This is particularly problematic in a chronic inflammatory disease like psoriasis, where long-term treatment adherence and cardiovascular comorbidity management are central to care. At minimum, these results should have been presented with greater caution and in full view of the totality of available evidence.

In conclusion, while the study raises an important question, its conclusions regarding cardiovascular safety—particularly for ixekizumab and ustekinumab—appear insufficiently supported by the available data and should, in our view, be interpreted with greater caution in light of existing clinical and real-world evidence.

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Declarations

Conflict of Interest. Tiago Torres has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, Amgen, Apogee Therapeutics, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Johnson & Johnson Innovative Medicine, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz, STADA and UCB. Luis Puig has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius-Kabi, Horizon (DSMB), J&J Innovative Medicine, Leo-Pharma, Lilly, Novartis, Pfizer, Samsung Bioepis, STADA, Sun-Pharma, Takeda, and UCB.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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