Journal Pre-proof

Comment on: “New Insights into the Evolution of Serum Calprotectin and Urinary CD163 in ANCA-Associated Vasculitis During Remission: an exploratory study”

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Title Page

Title — Comment on: "New Insights into the Evolution of Serum Calprotectin and Urinary CD163 in ANCA-Associated Vasculitis During Remission: an exploratory study"

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Manuscript

Comment on: "New Insights into the Evolution of Serum Calprotectin and Urinary CD163 in ANCA-Associated Vasculitis During Remission: an exploratory study"

Dear Editor,

The study by Martinez Valenzuela and colleagues addresses an important and clinically unresolved aspect of ANCA-associated vasculitis (AAV): how to interpret persistent immune activity during remission in patients receiving maintenance therapy [1]. By focusing on the longitudinal behavior of serum calprotectin and urinary soluble CD163, the authors move beyond cross-sectional assessments and contribute data that are directly relevant to day-to-day monitoring decisions in nephrology and vasculitis clinics.

A notable strength of this work lies in its emphasis on biomarker dynamics during stable remission rather than during overt disease activity. The observation that both calprotectin and urinary CD163 continue to evolve over time, despite a Birmingham Vasculitis Activity Score of zero, reinforces the concept that clinical remission may not equate to complete immunological quiescence [2]. This temporal dissociation has meaningful implications, as treatment decisions in remission are often binary continue or withdraw immunosuppression without reliable tools to capture smoldering disease biology. The data presented here suggest that serial biomarker trajectories may offer additional granularity beyond static thresholds.

The differential associations observed between the two biomarkers and clinical parameters merit particular attention. Serum calprotectin showed a consistent relationship with renal function indices, whereas urinary CD163 appeared more closely aligned with relapse risk, albeit modestly. This divergence supports the biological premise that these markers reflect distinct inflammatory compartments—systemic neutrophil–monocyte activation versus macrophage-driven renal inflammation. From a clinical perspective, this argues against reliance on a single biomarker and instead favors an integrated, pathway-informed interpretation when assessing residual disease activity in remission.

An especially relevant contribution of the study is the analysis of treatment-related effects on biomarker behavior. The finding that serum calprotectin levels vary according to the timing of rituximab administration, while urinary CD163 remains comparatively stable, underscores the need to contextualize biomarker values within therapeutic exposure. In patients receiving B-cell–depleting therapy, elevations in neutrophil-derived markers may reflect treatment-induced immune perturbations rather than disease reactivation [3]. This

distinction is critical, as misattribution could lead to unnecessary treatment escalation or premature retreatment.

The exploratory comparison with patients previously treated with mycophenolate mofetil further strengthens the argument that maintenance strategy itself shapes biomarker kinetics. Although not designed for formal comparative inference, the contrasting stability of biomarker levels in this group provides a useful clinical reference and highlights the complexity of interpreting immune markers across different therapeutic contexts.

Finally, this study raises a broader conceptual question regarding current remission definitions in AAV. The continued decline or fluctuation of biomarkers long after clinical remission suggests that existing frameworks may insufficiently capture ongoing immune processes relevant to long-term organ damage and relapse risk [4]. Incorporating longitudinal biomarker patterns into remission assessment could refine risk stratification and support more individualized maintenance strategies.

In summary, this work provides valuable insight into the nuanced behavior of calprotectin and urinary CD163 during remission and emphasizes the importance of temporal, treatment-aware biomarker interpretation. These findings may help inform future efforts to align immunological monitoring more closely with clinical decision-making in AAV, ultimately improving long-term renal and patient-centered outcomes.

Statements and Declarations:

- Declaration of Funding: No funding was received for this study.
- Conflict of Interests: The authors declare no conflict of interests relevant to this study.
- Ethical Approval: Not required.
- Clinical Trial Registration Details/Number: Not applicable, as this study does not report a clinical trial.
- Research Registry Number: Not applicable.
- Human Ethics and Consent to Participate Declarations: Not applicable as no patient data were collected or analyzed in this study.
- Generative Artificial Intelligence (AI) Use Statement: Generative AI tools, including Paperpal and ChatGPT-4o, were utilized solely for language, grammar, and stylistic refinement. These tools had no role in the conceptualization, data analysis, interpretation of results, or substantive content development of this manuscript. All intellectual contributions, data analysis, and scientific interpretations remain the sole work of the authors. The final content was critically reviewed and edited to ensure accuracy and originality. The authors take full responsibility for the accuracy, originality, and integrity of the work presented.

- Data Availability Statement: Not applicable, as no data were generated or analyzed in this study.

CRediT Author Statement:

- Kanishka Harariya: Validation, Writing—Original Draft, Writing—Review & Editing.
- Thakur Rohit Singh: Conceptualization, Methodology, Writing—Original Draft, Writing—Review & Editing.
- Ankita Kalra: Supervision, Project Administration, Writing—Original Draft, Writing—Review & Editing.
- Swarupanjali Padhi: Writing—Original Draft, Writing—Review & Editing.
- Fayaz Ahamed: Writing—Original Draft, Writing—Review & Editing.

All authors reviewed and approved the manuscript.

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Cover Letter

To
The Editor-in-Chief
NEFROLOGÍA

Dear Editor-in-Chief,

We are pleased to submit our manuscript entitled "Comment on: 'New Insights into the Evolution of Serum Calprotectin and Urinary CD163 in ANCA-Associated Vasculitis During Remission: an exploratory study'" for consideration for publication in *NEFROLOGÍA*.

In this study, we provide a focused and clinically grounded appraisal of the study by Martinez Valenzuela et al., with particular emphasis on the interpretation of biomarker dynamics during remission in ANCA-associated vasculitis. Our discussion centers on the implications of longitudinal behavior of serum calprotectin and urinary soluble CD163 for assessing persistent immune activity, renal involvement, and relapse risk in patients receiving maintenance therapy. We further examine how treatment-related effects, especially in the context of rituximab exposure, may influence biomarker interpretation and clinical decision-making during remission.

We believe this study will be of interest to the readership of *NEFROLOGÍA*, including nephrologists and clinician-scientists involved in the long-term management of vasculitis, as it contributes to ongoing discussions regarding biomarker-guided monitoring, remission assessment, and individualized maintenance strategies in AAV.

We confirm that this manuscript is original, has not been published elsewhere, and is not currently under consideration by another journal. We declare no conflicts of interest relating to this work. No funding was received for this study. All authors have contributed substantially to this work and approved the final version of the manuscript.

Thank you for considering our submission. We appreciate your time and look forward to your response.

Sincerely,

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On behalf of all the co-authors.