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RESPONSE TO LETTER

Interpreting Rituximab Response in Seronegative Membranous Nephropathy [Response to Letter]

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Dear editor

We appreciate the thoughtful comments from Cao et al[1] regarding our study,[2] published in *Drug design, development and therapy*. We appreciate their emphasis on the distinction between short-term antiproteinuric effects and durable immunologic remission, as well as the potential influence of rituximab (RTX) pharmacokinetics and immune monitoring on treatment outcomes.

In our study, we evaluated the efficacy of RTX versus non-RTX treatments (tacrolimus- or cyclophosphamide-based treatment combined with glucocorticoids) in patients with anti-PLA2R antibody-negative membranous nephropathy. Within the SAb-/GAg+ subgroup, the complete remission rates and overall response rates were significantly lower in the RTX group than in the non-RTX group (9.5% vs. 35.9%, $P = 0.024$; 57.1% vs. 81.1%, $P = 0.033$, respectively). We agree that the superior complete remission rate observed in the non-RTX group may partly reflect the rapid antiproteinuric effects of calcineurin inhibitors and glucocorticoids. As noted by Cao et al[1] these effects may not necessarily correspond to superior long-term immunologic disease control. Nevertheless, our findings remain clinically relevant because proteinuria reduction is an important therapeutic objective and predictor of renal prognosis in membranous nephropathy.

The RI-CYCLO randomized trial did not find that RTX offered greater benefits than cyclophosphamide-based therapy in membranous nephropathy, and the cyclophosphamide group included a higher proportion of anti-PLA2R antibodies-negative patients than the RTX group (41% vs. 27).[3] This observation supports the notion that other immunosuppressive strategies remain effective treatment options for this patient population. We also fully recognize the importance of RTX pharmacokinetics and immune monitoring. Factors such as urinary RTX loss, development of anti-RTX antibodies, inadequate B-cell depletion, timing of treatment, and retreatment strategies can significantly influence therapeutic outcomes. Unfortunately, due to the retrospective nature of this study, we were unable to routinely obtain serial data on peripheral blood B-cell counts, serum RTX concentrations, anti-RTX antibodies, or urinary drug loss. Therefore, we cannot rule out that the lower complete remission rate in some patients may have been due to insufficient RTX exposure.

In summary, our findings suggest that steroid-containing non-RTX regimens may achieve better short-term control of proteinuria in patients with SAb-/GAg+ membranous nephropathy. However, this does not imply that RTX is entirely unsuitable We concur with the authors' call for future prospective studies that integrate target antigen phenotyping with longitudinal pharmacokinetic and immunological monitoring. Only through long-term follow-up and individualized dosing strategies can the long-term efficacy of RTX in patients with serum anti-PLA2R antibody-negative membranous nephropathy be definitively established.

Disclosure

Yang Yang and Xiaojie Xie share first authorship for this communication. The authors declare that they have no competing interests in this communication.

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