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LETTER

Interpreting Rituximab Response in Seronegative Membranous Nephropathy [Letter]

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Dear editor

Yang et al[1] should be commended for addressing an important and underexplored question: whether rituximab remains suitable for patients with idiopathic membranous nephropathy who are seronegative for anti-PLA2R antibodies Their study suggests that non-rituximab immunosuppressive regimens may be associated with higher short-term complete remission and greater proteinuria reduction. This finding is clinically relevant, but two considerations may further refine its interpretation.

The observed advantage of non-rituximab therapy should be interpreted in light of the distinction between early antiproteinuric response and durable immunologic remission. In the SAb−/GAg+ subgroup, only 2 of 21 rituximab-treated patients achieved complete remission, compared with 19 of 53 patients receiving non-rituximab therapy. However, the non-rituximab group mainly received tacrolimus- or cyclophosphamide-based regimens, often with corticosteroids. Therefore, the study compares short-term outcomes across treatment regimens rather than establishing that rituximab itself is unsuitable for seronegative membranous nephropathy. Because calcineurin inhibitors may rapidly reduce proteinuria through podocyte-stabilizing and hemodynamic effects, early complete remission may not fully reflect long-term autoimmune disease modification.[2,3]

The study also underscores the importance of rituximab exposure and monitoring. Rituximab efficacy may depend on adequate B-cell depletion, sustained suppression of B-cell repopulation, urinary drug loss in nephrotic patients, anti-rituximab antibodies, and retreatment timing. Immunomonitoring studies in membranous nephropathy suggest that rituximab levels and B-cell kinetics may help identify patients at risk of early treatment failure.[4] Evidence from non-infectious uveitis further illustrates, in another immune-mediated setting, that rituximab outcomes may be shaped by treatment timing, maintenance strategy, and individualized monitoring rather than drug selection alone.[5]

Thus, Yang et al[1] raise an important hypothesis, but their data may be best interpreted as showing superior short-term proteinuria control with steroid-containing non-rituximab regimens Future studies integrating antigen-level phenotyping with serial immunologic and pharmacokinetic monitoring, and extending follow-up to relapse and treatment durability, would better clarify which seronegative patients remain suitable candidates for rituximab.

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