Membranous nephropathy: setting the bar for hypothesis-driven, selective therapies in nephrology

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Membranous nephropathy (MN) is a common glomerulopathy, especially in western countries where it accounts for more than one third of patients with nephrotic syndrome. MN is characterized by subepithelial deposition of podocyte targeted IgG4 antibodies. Autoantibodies reactive against Phospholipase A2 Receptor (PLA₂R) or, less commonly, thrombospondin type 1 domain containing 7A (THSD7A) are detected in 75–85% of primary MN patients [1]. Exostosin 1/exostosin 2, neural epidermal growth factor like-1 protein (NELL-1) and Semaphorin-3B were also recently identified as other putative podocyte antigens in MN [2].

Autoantibody deposition promotes glomerular basement membrane thickening, complement activation, and podocyte injury evidenced by proteinuria. The natural history of the untreated disease is variable: approximately one third of patients spontaneously remit, whereas 30% of cases develop end-stage kidney disease (ESKD) generally over 10–15 years. The remaining third have chronic proteinuria and persistent CKD [1].

Treatment approach for MN remains controversial. According to KDIGO-Review-Draft-June-2020 [3], immunosuppression should be started in the presence of decreasing eGFR or in case of life-threatening nephrotic syndrome. Treatment with alkylating agents accompanied by steroid pulses was the only regimen proven effective in preventing ESKD or death in patients with MN [3]. Clinical experience

and trial data established similar remission frequency with calcineurin inhibitors, but with a higher rate of relapse [3].

B cell central role in disease pathogenesis, both as precursors of autoantibody cells and as antigen presenting cells, provided rationale for B-cell depleting therapies [1]. After several case-reports and cohort studies described safety and efficacy of rituximab in MN, the GEMRITUX randomized trial compared anti-CD20 monoclonal antibody rituximab (two weekly doses of 375 mg/m²) plus conservative therapy vs. conservative therapy alone. The trial detected no significant difference in the primary end-point of complete or partial remission of proteinuria at 6 months. However, after a median follow-up of 17 months, rituximab was associated with higher remission rates than conservative treatment (64.9 vs. 34.2%) [4]. More recently, the noninferiority MENTOR trial (Membranous Nephropathy Trial of Rituximab) randomized patients to rituximab or cyclosporine [5] and reported significantly higher complete remission at 24 months in the rituximab group. This adds to increasing positive data making steroid-sparing B-cell depletion strategies attractive first-line therapies. Results from ongoing head-to-head studies with alkylating agents are eagerly awaited (NCT03018535–NCT01955187). Rituximab regimens vary, but common regimens include two infusions of 1 g repeated at 6 months to as little as a single dose of 375 mg/m².

In this issue of the Journal, Fenoglio and colleagues report a retrospective matched-control study [6] comparing the safety/efficacy profile of three different treatment regimens in 42 patients with MN: single-dose rituximab (375 mg/m²), four-dose rituximab (four weekly doses of 375 mg/m²), and cyclophosphamide alternating with corticosteroids. At 24 months, the rates of complete or partial remission were similar among the three groups ranging between 86 and 93%. Two patients who reached complete remission after single or four-dose rituximab relapsed at 32

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and 47 months of follow-up respectively, one patient treated with alkylating agents + steroids relapsed after 36 months. All three treatments were safe and no serious adverse events were reported. Based on these results, the authors conclude that rituximab is an effective alternative to alkylating agents, even with reduced dosages/frequency.

As pointed out by the authors, the retrospective nature of the study and the small sample size represent major limitations of this study. The fact that patients in the three study cohorts received treatment in different years also suggests a note of caution in interpreting these findings. In particular, data on anti-PLA₂R antibodies, the main biomarker of disease activity, are available only for patients treated with rituximab, challenging the interpretation of the results in patients treated with alkylating agents.

More importantly, follow-up period is short and may obscure more distant adverse events, especially from cyclophosphamide, commonly occurring years after drug exposure. Indeed, a previous larger retrospective, observational cohort study [7] comparing time to any adverse event (primary outcome) in 203 MN patients treated with rituximab ($n = 100$) or steroids plus cyclophosphamide ($n = 103$) found rituximab significantly safer than cyclophosphamide, with similar rates of complete remission. Of the 100 patients receiving rituximab (375 mg/m^2), 70 were treated with one dose and 30 with four weekly doses reporting no significant differences in terms of adverse events or complete remission.

The paper by Fenoglio points out the relevant issue of rituximab dose for MN. Initial dosing strategies for MN patients were based on treatment of non Hodgkin's lymphoma (375 mg/m^2 every week for 4 weeks), often followed by a second course at 6 months. Circulating CD20⁺ B cells are fully depleted already after the first rituximab administration and remain below normal range throughout 4 weeks of treatment. Three additional doses may not provide additional benefit, creating rationale for testing therapeutic efficacy of a single 375 mg/m^2 infusion. In a matched-cohort, single-center, controlled study, Cravedi et al. [8] compared the outcomes of 12 incident patients with MN receiving single rituximab doses with 24 matched control patients receiving four weekly doses. At 12 months, complete remission was similar in both groups (25%) and only 1 patient who received low dose needed a second treatment. Adverse events occurred in three standard protocol patients during their second infusion of rituximab. Moreover, one subjects who received the standard protocol, reported severe systemic rash during the second course, causing the interruption of treatment of the recurrence.

Minimizing rituximab dosages prevents infusion events as well as treatment resistance. Boyer-Souavet et al. [9] studied development of anti-rituximab antibodies. These authors described 17 MN patients receiving second rituximab courses at a median time of 12 months after the first

treatment with two 1 g infusions of rituximab at 2 weeks interval. Anti-rituximab antibodies were reported in 10 patients and were significantly associated with faster B-cell reconstitution at 6 month and higher proteinuria at 12 months of follow-up. Moreover, relapse rates were significantly higher in patients developing anti-rituximab antibodies. Of note, three patients with anti-rituximab antibodies were successfully treated with anti-CD20 fully human antibody, ofatumumab.

Altogether, these data support the findings by Fenoglio et al. [6] and provide compelling rationale that use of lower dosage rituximab regimens have less side effects than alternative regimens/agents while being, at least, equally efficacious.

Despite its benefits, rituximab does not successfully treat all MN cases. Long-lived plasma cells reside primarily in bone marrow and produce autoantibodies independently of B-cell depletion. Plasma cells, unaffected by anti-CD20 therapies, are targeted with anti-CD38 antibodies, such as daratumumab and isatuximab, originally developed for treating plasma cell malignancies. An on-going phase 2, open-label, multi-center study is testing the safety and efficacy of human anti-CD38 antibody MOR202 in adults with anti-PLA₂R-specific antibody MN (NCT04145440). Proteasome inhibitors also deplete plasma cells. Bortezomib causes intracellular accumulation of abnormal proteins leading to apoptosis. Limited case reports describe the efficacy of bortezomib in MN patients, with no lymphoproliferative disorders.

Belimumab, a human monoclonal antibody against B-lymphocyte stimulator (BLyS) inhibitor, is approved for treatment of seropositive systemic lupus erythematosus (SLE), reducing both disease activity and autoantibody levels. In a prospective case-control study enrolling 14 patients with MN, Belimumab administered up to 2 years effectively reduced anti-PLA₂R-specific antibodies and proteinuria. In 11 participants completing 28 weeks of follow-up, 9 experienced total or partial remission. These encouraging findings provide support for further studies of belimumab for MN.

An untested but intriguing possibility involves engineering of T cells with chimeric antigen receptor technology. US Food and Drug Administration recently approved administration of chimeric antigen receptor T cells (CAR-T) to treat B cell lymphomas and leukemias. Therapy involves genetically engineered autologous T cells with HLA-independent recognition of target antigens. Autologous T cells are obtained via leukapheresis and fusion protein CAR expression is induced via viral transduction: CAR DNA codes for antibody fragments that promote antigen specific killing. Theoretically, CAR T cells can target pathogenic autoreactive B cells, e.g. those targeting PLA₂R. Advantages of this approach include more profound and prolonged B cell depletion compared to current anti-B cell monoclonals.

In conclusion, research on MN has been a successful story, in which basic science studies of disease pathophysiology directly translated to hypothesis-driven therapeutic strategies that, in turn, further increased understanding of pathogenesis. The ever-improving strategies to treat MN represent a successful therapeutic paradigm for nephrology, in general, based on principles of hypothesis-driven precision medicine.

Compliance with ethical standards

Conflict of interest Authors declare no conflicts of interest.

Ethical statement This editorial doesn't contain any studies with human participants or animals performed by any of the authors.

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