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Rituximab is preferable to cyclophosphamide for treatment of membranous nephropathy: PRO

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Primary membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults. This histologic pattern is related to circulating autoantibodies against the M-type antigen phospholipase A2 receptor (PLA2R) in over 70% of patients with primary MN. Patients with non PLA2R-associated and primary MN may be positive for other target antigens such as thrombospondin type-1 domain-containing 7A (THSD7A), neural epidermal growth factor-like 1 (NELL-1), or semaphorin 3B (Sema3B) (1). Spontaneous remission of proteinuria can occur in 1 of every 3 cases and is associated with excellent long-term outcomes; in contrast, end-stage kidney disease may occur in approximately 35% of cases untreated that remain nephrotic at 10-years follow-up (1). Some factors, such as high levels of anti-PLA2R antibody at the time of diagnosis (≥150 RU/mL by the ELISA method), non-declining or increasing titers, protein excretion that exceeds 8-10 grams per day, or a decrease in kidney function are related with lower risk of spontaneous remission and progression of disease, in which case immunosuppressive therapy is recommended. Anti-PLA2R measurements have come to play a crucial role informing patients and their nephrologists of the immunological status of disease to guide treatment decisions (2).

Cytoxic agents combined with corticosteroids have been considered a gold standard therapy in primary membranous nephropathy for many years despite their significant adverse event profile (2) possibly under reported in classical studies. The use of alkylating agents has been associated with increased risk of malignancy, bladder and gonadal toxicity, infertility, bone marrow toxicity, dermatologic side effects and opportunistic infections among others, prompting a continued search for equally effective but less toxic therapeutic options (2). This profile of side effects requires close monitoring for leukopenia, admissions because of complications, increasing costs not usually mentioned. Rituximab (RTX) is a monoclonal antibody directed against CD20 that depletes B cells. Early case reports demonstrated that four weekly infusions of

rituximab (375 mg/m^2) were capable of reducing proteinuria in idiopathic membranous nephropathy with treatment-refractory nephrotic syndrome (3) and also as first line therapy in patients who did not achieve spontaneous remission with supportive treatment (4). These early reports, with follow-up periods ranging from 20 weeks to 1 years, were incomplete, as long-term studies in membranous nephropathy have demonstrated that effectiveness in therapy should be evaluated over a longer duration follow-up, with proteinuria nadir not being reached until more than 2 years after the start of therapy (5).

Fervenza et al. (6) subsequently studied different dose administrations of RTX and outcomes at 24-months in patients with primary membranous nephropathy. Four weekly infusions of 375mg/m^2 RTX with re-treatment at 6 months were compared with 1 g RTX at day 0 and 15 with retreatment at month 6. The four-weekly dose regimen resulted in more effective B cell depletion, but proteinuria reduction was similar to RTX at 1 g every 2 weeks at 24 months follow up (6). Beck et al. (7) evaluated the immunological response to rituximab with anti-PLA2R measurements before and after treatment in 35 patients with primary membranous nephropathy. Nadir levels of anti-PLA2R antibodies were achieved in 68% of patients within 12 months of treatment and preceded decline in proteinuria by 24 months in most cases (7). Dahan et al. compared immunological remissions at month 6 between rituximab and alkylating agents; this initially non-favorable study for RTX at month 6 was re-evaluated after 19.5 months of follow up, and after a re-dose of RTX, most patients had achieved immunological remission (80%) and all had achieved some form of clinical remission (8). These early series suggested a clear and effective role of utilizing RTX for treating MN, guided by immunologic status of disease, but data from large-scale randomized controlled trials (RCTs) were still required to definitively position RTX as the optimal 1st line immunosuppressive agent for MN.

The RCTs of rituximab in primary membranous nephropathy, by order of reporting, have been the Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX) trial (9), the MEmbranous Nephropathy Trial Of Rituximab (MENTOR) (10), the Sequential Therapy with Tacrolimus and RTX in Primary MN (STARMEN) trial (11) and the Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO) trial (12). The GEMRITUX trial (9) included 75 biopsy-proven MN patients with persistent proteinuria greater than 3.5 g/day after six months of supportive care who were were randomly assigned to RTX (two infusions of 375 mg/m2 administered one week apart) or placebo. At six months, there was no significant difference in the primary composite endpoint of complete or partial remission of proteinuria between patients treated with or without rituximab. Anti-PLA2R antibodies, which were present in 73 percent of patients at baseline, disappeared in a greater proportion receiving RTX (50 versus 12 percent), demonstrating a marked improvement in immunologic remission for those treated with RTX. As mentioned above, a 6-month evaluation may be too early to evaluate proteinuria-based outcomes in membranous nephropathy. Indeed, at last follow-up reported in this study (median 17 months), RTX demonstrated almost twice the rate of complete or partial remission (65%) compared to placebo (34%) ($p<0.01$ for comparison).

The MENTOR trial (10) included 130 patients with proteinuria ≥5 g/day and 24-hour creatinine clearance ≥40 mL/min/1.73 m2 after at least three months of supportive care who were randomly assigned to RTX (1 g administered 14 days apart, repeated at six months in case of partial response) or oral cyclosporine (3.5 mg/kg per day for six months, or 12 months in case of partial response at six months, with dose adjustment to maintain a 12-hour trough concentration of 125 to 175 ng/mL). The primary endpoint was a composite of complete (proteinuria <0.3 g/day and serum albumin ≥3.5 g/dL) or partial (reduction in proteinuria ≥50% and final proteinuria between 0.3 and 3.5 g/day)

remission at 24 months. At 24 months, patients receiving rituximab had a higher rate of complete or partial remission than those receiving cyclosporine (60% versus 20%, respectively); only patients receiving rituximab achieved complete remission (35% versus 0% in the cyclosporine group). In addition, the estimated glomerular filtration rate was higher in the RTX group at the end of the study (100 versus 87 mL/min/1.73 m2 at 24 months). Anti-PLA2R antibody levels fell more rapidly with sustained clearance in the RTX group, explaining a very low rate of relapses (5%).

The STARMEN trial (11) was a randomized, open-label controlled trial of 86 patients with primary MN. After 6 months of supportive care, the study assigned 43 patients to receive six-month of cyclical treatment with corticosteroid and cyclophosphamide and 43 patients to receive 6 months with tacrolimus followed by one dose of RTX (1 g). The primary endpoint – complete or partial remission of nephrotic syndrome at 24 months – was significantly higher in the cyclophosphamide group (83.7% versus 58.1%). Complete remission at month 24 occurred in 60% of patients with cyclophosphamide/steroids versus 26% of patients in the tacrolimus–RTX group. Notably, baseline median levels of anti-PLA2R antibodies in the tacrolimus-RTX group were higher (113 RU/ml versus 59 RU/ml in the cyclophosphamide arm), and rates of immunologic response at 24 months were similar between the groups (83% in the tacrolimus-RTX patients vs 88% in the cyclophosphamide/steroids patients). Serious adverse events were similar in both groups. While the STARMEN trial has been interpreted as a “negative” study for RTX, the similar rates of immunologic remission suggest that over a longer period of follow-up results between the two groups may be comparable. In addition, the role of RTX monotherapy cannot be evaluated in this study as the drug was dosed after 6 months of tacrolimus and at a lower dose than typically used for MN therapy.

The RI-CYCLO trial (12), was an open-label controlled trial of 74 patients randomized to RTX (1g two weeks apart) or corticosteroid-cyclophosphamide regimen after a run in of at least 3 months. Complete remission was defined as proteinuria ≤0.3 g/day, partial remission as a reduction of proteinuria >50% and an absolute value of 0.3-3.5 g/day. The primary end-point of the study, complete remission at 12 months, was achieved in 16% in the RTX group versus 32% in the CYC arm. Interestingly, at month 24 outcomes were similar: 62% in the RTX arm had achieved complete or partial remission vs. 73% in the CYC arm. The probability of complete remission alone at 24 months was also similar in both groups, with no differences in side effects. According to data previous RI-CYCLO trial, from comparable randomized controlled trials at month 24, rituximab compared to cyclophosphamide/steroids could have superior rates of percentage of complete remission (35% versus 20%) with lower relapse rates 5% vs. 25% (13).

Taken together, the data from the RCTs of RTX in MN further support the findings from earlier case studies. For patients with primary MN who did not achieve spontaneous remission, RTX is able to induce an immunologic remission at 6 to 12 months: earlier in patients with lower PLA2R antibodies and milder disease, later in patients with higher PLA2R antibodies who will typically require re-dosing of RTX. These immunologic remissions anticipate clinical remissions that will occur 3-12 months later. In viewing the disease course of MN as a marathon rather than a sprint, RTX emerges as an ideal first line agent given its ability to achieve response in up to 80% of patients over sufficient periods of follow-up. While this efficacy is similar to cyclophosphamide-based regimens, the results come via a steroid-free regimen with an overall better side effect profile and, as an intravenous agent dosed every 6 months, no concerns over treatment adherence. For these reasons, we are firmly in the era of RTX as the preferred immunosuppressive therapy for MN. And this era is expected to last until

something even better – perhaps in the form of even more effective B cell depletion with obinutuzumab – comes along.

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AUTHOR CONTRIBUTIONS

A Bomback: Writing - original draft; Writing - review and editing

N Oliva-Damaso: Writing - original draft

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