Management of Membranous Nephropathy after MENTOR

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Membranous nephropathy is a common cause of primary nephrotic syndrome, yet it can be particularly vexing to treat due to its extended duration and uncertainties about the implications of a partial remission. Ten years ago, the phospholipase A2 receptor (PLA2R) was identified as the major target antigen in primary membranous nephropathy (1), and the monitoring of antiphospholipase A2 receptor autoantibodies (PLA2R-Abs), a surrogate of immunologic activity, has ushered in a new era for disease diagnosis and treatment. In this timeframe, we have recognized the utility of a serologic approach to membranous nephropathy and have come to better understand the genetics and epitopes that underlie the humoral response to PLA2R, but we remain with limited information about optimal treatment. The recent Membranous Nephropathy Trial of Rituximab (MENTOR) study (2), comparing the B cell–depleting agent rituximab with cyclosporin for the treatment of primary membranous nephropathy, now provides important insights in this last realm.

The slow-to-form, slower-to-resolve immune deposits dictate that changes in clinical signs (proteinuria and serum albumin) lag behind changes in humoral immune activity. Remissions in membranous nephropathy may take years, typically progressing from partial to complete remission in the absence of chronic tissue damage. Clinical trials limited to ≤24 months may not fully capture all patients responding to treatment when only clinical parameters are measured, because immunologic responses may not have translated into clinical remissions. Our best evidence about remission rates and progression to kidney failure comes from studies using alkylating agents alternating with corticosteroids (Ponticelli regimen) with 10 years of follow-up. On the basis of this evidence, the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines rate this treatment regimen as first line. As an alternative, KDIGO recommends the use of calcineurin inhibitors, which in addition to their immunosuppressive actions, also have complementary (or confounding) effects on proteinuria.

Because of the role of B cells in autoantibody production in membranous nephropathy combined with adverse effects of alkylating agents, corticosteroids, and calcineurin inhibitors, increasing amounts of observational data have emerged about the effectiveness of rituximab. A lack of randomized, controlled trials, however, precluded consideration of rituximab as a first-line agent. This has now clearly changed with the MENTOR study and will have implications for future guidelines and patient access to this drug.

Several points about the MENTOR protocol are worth noting. Sustained proteinuria of >5 g/d was required for a minimum of only 3 months as was a relatively preserved eGFR of ≥40 ml/min per 1.73 m^2. The initial cycle of rituximab (1000 mg; days 1 and 15) was repeated at 6 months unless complete remission had already occurred. Similarly, cyclosporin was administered at therapeutic levels for 6 months, but it was extended for another 6 months in the absence of complete remission. Cyclosporin was tapered off over a subsequent 2 months. In either arm, the subject was removed from the study as a treatment failure if proteinuria was reduced by <25% at 6 months. The authors acknowledge that this might have prematurely removed subjects with an immunologic response who had not yet manifested a proteinuric response.

The primary outcome in the MENTOR study was a composite of complete/partial remissions at 24 months. Rituximab demonstrated noninferiority at 12 months, with 60% of patients achieving remission in the rituximab group versus 52% in the cyclosporin group. This initial similarity in remission rate deteriorated after 12 months due to a large number of relapses after cyclosporin was stopped. At 24 months, rituximab exhibited statistical superiority, with achievement of complete/partial remission in 60% in that group versus 20% with cyclosporin.

Although any remission is better than none, the goal in the treatment of membranous nephropathy should be complete remission, which may take longer than 24 months to achieve. Significant differences in complete remission rates between the two arms of the MENTOR study were observed. With rituximab, a total of 39 patients achieved remission by 24 months, 23 of whom achieved complete remission; 18 of these 23 complete responders were PLA2R-Ab positive at baseline, and all achieved immunologic remission by 24 months. In contrast, although three complete remissions occurred in the cyclosporin group by 12 months, none remained in complete remission at 24 months; the 13 responders at this point had only achieved partial remission.

The MENTOR study has numerous important clinical implications and raises the following questions.

(*1*) Which agents should be considered first line in membranous nephropathy?

The MENTOR study has confirmed in a randomized, controlled trial that rituximab is efficacious and able to bring about durable remission in the majority of patients with an acceptable safety profile. Because of poor performance of cyclosporin, the MENTOR study suggests that rituximab should be the recommended alternative agent for the treatment of membranous nephropathy when alkylating agents are not suitable (*e.g.*, in women of child-bearing age, those with increased cancer risk due to tobacco exposure, and prior cyclophosphamide).

Calcineurin inhibitors no longer seem suitable as first-line agents for membranous nephropathy. Although they can effectively reduce proteinuria, high rates of relapse after withdrawal make them poor treatment choices. Their use should be restricted to situations when other drugs are not available or contraindicated. A potential role as an adjunctive agent with other immunosuppressants remains viable; the STARMEN trial (NCT01955187) that compares the modified Ponticelli regimen with a combination of tacrolimus with rituximab will provide important additional data.

Although historical comparison of rituximab with alkylating agents has suggested that cyclophosphamide should also be dethroned as the first-line agent in primary membranous due to its serious side effect profile (3), it should be remembered that the dosing of cyclophosphamide used in this study exceeded that of the standard modified Ponticelli regimen. An ongoing study (the RI-CYCLO; NCT03018535) seeks to address the relative efficacy of rituximab to the modified Ponticelli regimen; however, only 76 patients have been recruited, and therefore, results may be limited.

(*2*) What dosing protocol is optimal for the use of rituximab in membranous nephropathy?

The dosing of rituximab in the MENTOR study is similar to the protocol used in the NICE cohort, and it is significantly higher than the cumulative dose received by patients from the GEMRITUX cohort (two 375-mg/m^2 infusions 1 week apart) (4). A comparison of these last two cohorts showed that the higher-dose protocol achieved more immunologic and clinical remissions (5). Rituximab loss into nephrotic urine with insufficient initial dosing may result in subtherapeutic drug levels, and indeed, residual plasma rituximab levels at 3 months were lower in the GEMRITUX cohort compared with the NICE cohort (5). The field awaits further studies and recommendations guiding the dosing of rituximab in terms of level of nephrosis, autoantibody titer, and dynamic changes in B cells.

(*3*) What is the safety profile of rituximab?

The most common side effects in the MENTOR study were infusion-related reactions. No specific infection prophylaxis was used, and infection rate was not increased compared with the cyclosporin group. No patients with opportunistic infection were reported. This milder side effect profile of rituximab was also noted in a historical comparison with cyclophosphamide/steroids (3).

(*4*) How can we best use circulating autoantibody levels when treating with rituximab?

Monitoring PLA2R-Ab levels to assess immunologic remission and predict clinical response has become routine practice. The MENTOR study included 96 PLA2R-Ab–positive subjects (74%) who were monitored by ELISA (note that reported titers from this assay are not directly comparable with the more commonly used commercial ELISA). Previous studies with rituximab have demonstrated an early and sustained drop in PLA2R-Ab preceding favorable clinical response, whereas incomplete suppression of PLA2R-Ab was not associated with remission (6,7).

In both the GEMRITUX cohort (rituximab versus supportive antiproteinuric therapy) and the MENTOR study, clinical remission rates did not significantly differ between arms at 6 months, yet rituximab induced a higher "immunological remission rate" (undetectable PLA2R-Ab) at 6 months (2,4). These increased rates of immunologic remissions persisted beyond 6 months in the rituximab arm of the MENTOR study. Of note, the one THSD7A-Ab–positive subject in the MENTOR study followed a similar course after rituximab treatment: antibody disappeared by month 3 followed by complete remission. It is clear that rituximab has considerably different efficacy versus cyclosporin in achieving durable suppression of circulating PLA2R-Abs; PLA2R-Ab tends to rebound after calcineurin inhibitor cessation. It is unknown whether extended duration treatment tailored to autoantibody levels would prevent such a rebound.

It is unfortunate that subjects were considered treatment failures at 6 months if they had not achieved a ≥25% reduction in proteinuria. Such patients had higher baseline PLA2R-Ab titers and were less likely to achieve immunologic remission by 6 months. Complete elimination of high-titer PLA2R-Ab would not necessarily be expected by 6 months, and in clinical practice, such patients demonstrating a significant drop in PLA2R-Ab would likely be redosed with additional rituximab. Although these subjects were technically treatment failures per the MENTOR protocol, it would be of interest to know how many of them had significant drops in autoantibody titer that might have predicted treatment success had they remained in the study.

Higher PLA2R-Ab titer has been associated with the presence of autoantibodies reactive with epitopes in PLA2R beyond the immunodominant N-terminal epitope, a process called epitope spreading (5,8). "Spreader" patients achieve spontaneous remission less often and tend to have worse clinical outcomes. Initial data suggested that cyclophosphamide might be more effective in patients with high titers of PLA2R-Ab (9); however, retreatment with additional rituximab was able to alleviate this apparent resistance (10).

In summary, the MENTOR study establishes superiority of rituximab over cyclosporin and places rituximab as a (or perhaps "the") first-line agent for membranous nephropathy. Roles for cyclophosphamide and calcineurin inhibitors require critical re-evaluation, and how best to use baseline PLA2R-Ab or epitope spreading to guide treatment decisions remains to be determined. We look forward to another exciting decade of membranous nephropathy!

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