Membranous nephropathy (MN) is a common immune-mediated glomerular disease and one of the leading causes of nephrotic syndrome in Caucasian adults (1). Although in most patients the disease progresses relatively slowly, approximately 40% of patients eventually develop ESRD (2). This is particularly true for patients who remain nephrotic despite therapy (3). Several immunosuppressive treatments seem to be at least partially successful in reducing proteinuria in MN (recently reviewed in reference [4]); however, their use can be associated with a number of adverse effects, an issue that is important with a disease for which up to 30% of patients are said to achieve spontaneous remission of proteinuria and will enjoy long-term renal survival. This problem of drug toxicity can be exemplified by the use of calcineurin inhibitors (CNI; e.g., cyclosporine, tacrolimus). In patients with MN, prospective, randomized studies with the use of CNI have demonstrated that these agents can induce remission of proteinuria (either complete or partial remission) in >70% (5–7). For reaping their maximum benefit, current recommendations are that these agents be used for a prolonged period (e.g., ≥12 mo) (8). Prolonged CNI treatment, however, can be complicated by a number of adverse effects, including hypertension and nephrotoxicity, the latter being dosage/duration dependent as well as age dependent. An additional problem with CNI is that almost half of patients’ disease will relapse once the drug is withdrawn (5–7,9). Prolonged low-dosage CNI could be considered for long-term maintenance of patients who are CNI dependent, with seemingly little risk of nephrotoxicity, but the risk is certainly not zero and may require using repeat renal biopsy surveillance (9).

In this issue of *CJASN*, Segarra et al. (10) give us an alternative treatment option for patients who have MN and are CNI dependent: Rituximab. This is not surprising, because a few uncontrolled studies suggested that rituximab is effective in reducing proteinuria in most patients with MN (2,11–14). In this observational study, Segarra et al. treated 13 patients who had idiopathic MN and preserved renal function and were deemed dependent on a CNI with four weekly doses of rituximab (375 mg/m² each dose). After rituximab treatment, withdrawal of CNI and other immunosuppressant drugs (mycophenolate mofetil and corticosteroids) was possible for all patients. At 12 mo, four patients remained in complete and nine in partial remission. Three patients experienced a relapse of nephrotic-range proteinuria 19, 23, and 28 mo after rituximab treatment and were successfully treated with a second course of rituximab. All patients remained in partial remission after a minimum follow-up period of 30 mo. The authors concluded that in patients who have MN who are CNI dependent, rituximab therapy offers an effective tool to overcome CNI dependence. Rituximab allows the avoidance of the nephrotoxicity that is associated with the prolonged use of CNI while at the same time maintains a long-lasting remission of proteinuria.

Unfortunately, as pointed out by the authors, the study was purely observational and not conducted in a controlled manner. The lack of a control group makes it difficult to rule out completely the possibility that some patients had gone into spontaneous remission, especially because all patients were in partial remission at the time of initiation of rituximab treatment. Although the authors argue that this possibility is unlikely in view that all patients had been followed for a long time and were clearly CNI dependent, it cannot be ruled out. Information is also lacking regarding the patients’ characteristics before their initial course of CNI. For example, data on the severity of proteinuria (moderate [5 g/24 h] or severe [≥8 g/24 h]) before initiation of CNI were not provided. In addition, it is difficult to ascertain whether all patients were indeed CNI dependent. As per protocol, CNI dependence was defined as the occurrence of at least four relapses of nephrotic syndrome while being tapered off these drugs; however, at least three patients had been on a CNI for a period of ≤24 mo. Thus, we can assume that at least in some patients, CNI withdrawal was initiated as soon as they achieved remission. Because no information is given regarding the time-dependent changes in proteinuria after initiation and discontinuation of CNI treatment, we cannot make meaningful comparisons with the data after rituximab treatment. As pointed out already, current recommendations regarding the use of CNI are based on observations that in patients with MN, prolonging treatment with CNI (≥1 yr) results in higher and more sustained rates of remission (7,15). Short-term courses of CNI therapy may explain why the majority of the patients were in partial remission and why patients in partial remission were more likely to experience relapse when CNI were discontinued. As presented, however,
the data do not allow us to conclude that all patients were definitely and persistently CNI dependent at the time of entry into the study.

The use of rituximab was justified on the basis of the risk for nephrotoxicity associated with the prolonged use of CNI in these patients. Indeed, before rituximab treatment, nine patients underwent repeat renal biopsy, and, in these patients, a significant increase in the percentage of both glomerular and interstitial sclerosis was observed; however, given the long time interval between the first and second biopsies, a number of other variables, such as age, persistence of proteinuria, and degree of BP control, could by themselves explain the renal biopsy findings. We are not given any information regarding the dosages of CNI used to treat the relapses, the duration of such initial dosages, the serum levels achieved, etc., data that are crucial in ascertaining the nephrotoxicity of these agents. This information is important in view of recent data by Alexopoulos et al. (9) showing that long-term treatment with low-dosage cyclosporine in patients with MN is associated with low risk for nephrotoxicity. It is also crucial if we want to explain why in some patients subsequent biopsy samples showed 0% of sclerosed glomeruli and 0% of interstitial fibrosis even after prolonged course of CNI therapy.

An important observation of the study is that patients who achieved a remission with rituximab can have a relapse of their proteinuria. Thus, at least in some patients, rituximab can induce remission of proteinuria, but it does not “cure” the disease, stressing the need for long-term follow-up for these patients. A second course of rituximab was effective in inducing remission, but reexposure to rituximab has the potential to induce the production of human anti-chimeric antibodies (HACA). Because patients in this study were not tested for HACA, the development of HACA is unknown. Formation of HACA after rituximab therapy is uncommon (16) and may be related to effect of rituximab in abolishing primary and memory humoral responses (17). Conversely, the underlying disease itself may affect the propensity for antibody formation as illustrated by detectable HACA in 30% of patients who had systemic lupus erythematosus and were treated with rituximab (18). The development of HACA may also be related to the dosage of rituximab, which may have an impact on the degree of B cell depletion. For example, HACA developed in six (43%) of 14 patients who had MN and were treated with two doses (1 g each) of rituximab (11); however, HACA has not occurred in any of the 20 patients who had MN and were enrolled in a recently completed study and who received four weekly doses of rituximab (375 mg/m² each) (F.C.F. et al., unpublished observations). Although such antibodies are not associated with clinical symptoms, after repeated drug administration, they may increase the risk for hypersensitivity reactions, retard B cell depletion, and limit the effect of rituximab in patients who need re-treatment (18,19). This issue may acquire more relevance in face of recent reports suggesting that a single dose of rituximab could be as effective as four weekly doses in inducing remission of proteinuria in patients with MN (14). This of course could become a moot point once the humanized version of rituximab becomes available, so time will tell.

Despite the potential criticisms, the study of Segarra et al. (10) adds to the number of uncontrolled case series suggesting a beneficial effect of rituximab in the treatment of MN. Similar to previous reports, rituximab was well tolerated and no significant adverse effects were observed. It needs to be pointed out, however, that the risk for complications, such as progressive multifocal leukoencephalopathy, is likely to increase according cumulative immunosuppression used in a specific patient. Thus, although rituximab has seemed to be safe when used in a patients with no or little previous immunosuppression exposure, the same may not hold to be true for patients who have previously undergone repeated and/or prolonged courses of immunosuppression therapy.

As pointed out by the authors, it is important that these encouraging results be confirmed by adequately powered, randomized, controlled studies before recommendations can be made regarding the use of rituximab in patients with MN. Further research is also needed to explain the mechanism of action of rituximab in inducing remission of proteinuria in MN. Both experimental and human studies have shown that MN is mediated by deposition of IgG antibodies in the subepithelial area of the glomerular basement membrane. Data from animal studies suggest that immune deposition resulting from B cell activation promotes injury to the glomerular filtering barrier resulting in proteinuria. In humans, there is evidence that therapy directed against B cells (e.g., cyclophosphamide, which has striking but nonselective effects on B cell function and suppresses the secretion of Ig) is effective in MN (20). Given the key role of IgG antibodies in MN, it is reasonable to postulate that suppression of the pathogenic antibody production by depleting B cells with rituximab may explain the improvement in the glomerular pathology as reflected by a reduction in proteinuria. For example, Salant’s (21) group recently showed that sera from approximately 70% of patients with MN specifically detect a 200-kD human glomerular antigen identified as the M-type phospholipase A2 receptor. Does rituximab treatment affect the production of these antibodies? Does disappearance of the antibodies correlate with the clinical response? The effect of rituximab on B cells is unlikely to be the solely explanation for the benefits observed in patients with MN. Despite confirmed B cell depletion in all studies, only 60 to 70% of the patients with MN will respond to rituximab therapy. Rituximab disrupts T and B cell communications and may have other independent effects still unknown. Some patients whose disease fails to respond to a first course will respond to a second course of rituximab. Failure to respond to rituximab does not preclude response to immunosuppressive agents that target T cells (e.g., CNI [Dan Cattran, Renal Unit, University of Toronto, Toronto, Ontario, Canada, personal communication, April 2009]). This suggests that although renal biopsies may look the same, the pathophysiology of the disease is likely to vary. A better understanding of the pathophysiology of MN may also help us to identify a priori which patients are likely to benefit from rituximab treatment. Research in this area is sure to keep us entertained for the next few years.
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References