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Membranous Nephropathy: Pilot Study of a Novel Regimen Combining Cyclosporine and Rituximab

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Introduction: There is broad consensus that high-grade basal proteinuria and failure to achieve remission of proteinuria are key determinants of adverse renal prognosis in patients with primary membranous nephropathy. Since current regimens are not ideal due to short- and long-term toxicity and propensity to relapse after treatment withdrawal, we developed a treatment protocol based on a novel combination of rituximab and cyclosporine that targets both the B-cell and T-cell limbs of the immune system. Herein, we report pilot study data on proteinuria and changes in autoantibody levels and renal function that offer a potentially effective new approach to treatment of severe membranous nephropathy.

Methods: Thirteen high-risk patients defined by sustained high-grade proteinuria (mean 10.8 g/d) received combination induction therapy with rituximab plus cyclosporine for 6 months, followed by a second cycle of rituximab and tapering of cyclosporine during an 18-month maintenance phase.

Results: Mean proteinuria decreased by 65% at 3 months and by 80% at 6 months. Combined complete or partial remission was achieved in 92% of patients by 9 months; 54% achieved complete remission at 12 months. Two patients relapsed during the trial. All patients with autoantibodies to PLA_2R achieved antibody depletion. Renal function stabilized. The regimen was well tolerated.

Discussion: We report these encouraging preliminary results for their potential value to other investigators needing prospectively collected data to inform the design and power calculations of future randomized clinical trials. Such trials will be needed to formally compare this novel regimen to current therapies for membranous nephropathy.

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Primary membranous nephropathy (MN) is an autoimmune disorder caused by antibodies to constitutive antigens of glomerular podocytes.[1,2] Cell surface antigen–antibody complexes are capped into aggregates and shed from podocytes where they bind to and accumulate along the external lamina of the glomerular basement membrane. Complement is activated by the immune complexes and is a key factor leading to the glomerular proteinuria.

The natural history of MN is variable[3–5] and likely depends on ambient levels of circulating pathogenic autoantibodies. Remissions can occur spontaneously,[4,5] presumably by restoration of autoregulation of normal antibody production, or can be gained by treatment-induced suppression of pathogenic autoantibodies. Approximately one-quarter of patients with MN undergo spontaneous remission, while the vast majority are prone to persistent high-grade proteinuria, approximately one-half of whom are at risk of progression to renal failure.[6]

Given the potential toxicities of traditional immunomodulatory drugs, decisions regarding therapy must take into account the natural history of the disease and objective efficacy of the various therapeutic options balanced against the risks of protracted nephrotic syndrome (NS) and loss of renal function, as well as risks of drug toxicities. Current guidelines support limiting the use of immunosuppressive treatment to

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patients who are considered at medium and high risk of progression to end-stage kidney disease (ESKD) based on clinical observations acquired over time.[6–9] Accepted treatment options include combination therapy with glucocorticoids and a cytotoxic alkylating agent or calcineurin inhibitors (CNIs).[9] Cytotoxic-based regimens are often considered as first-line therapy for patients at high risk of progression,[9,10] but potential short- and long-term adverse effects of cytotoxic drugs (bone marrow suppression, infertility, as well as infection and malignancy diathesis with greater cumulative exposure) greatly influence therapeutic decisions.[11,12] CNIs lead to earlier reductions in proteinuria but are associated with high relapse rates (occurring in almost 50% within a year of drug withdrawal);[13–16] these considerations usually lead to prolonged therapy with its attendant risks, particularly nephrotoxicity. In the continued search for new treatments that might offer higher therapeutic indices, there has been growing enthusiasm for use of the B cell–depleting agent rituximab for MN based on the central role in disease pathogenesis of IgG autoantibodies to M-type phospholipase A_2 receptor (PLA_2R),[17] and other glomerular antigens.[18,19] Encouraging results from case series and uncontrolled pilot trials of rituximab have been reported.[20–24] However, small series reported to date show mostly delayed and partial remissions of NS, as well as a propensity to relapse after single courses of rituximab.

In an effort to overcome these unresolved issues and limitations of conventional therapies for MN, we initiated a prospective single-arm pilot study to investigate whether "induction" treatment with the combination of rituximab plus a 6-month course of cyclosporine followed by a "maintenance" course of rituximab might lead to earlier, more complete and durable clinical and immunologic remissions of MN than either agent alone. We hypothesized that cyclosporine and rituximab would act synergistically, as they have different effects on the immune system (T and B cells, respectively) and on the podocyte, and distinct onset of action (early vs. delayed, respectively) as well as duration of action. We envisioned that such pilot studies were necessary to acquire data that would inform the design and power calculations for testing rituximab-based combination therapies in the future. We considered that the preliminary results regarding safety and efficacy of this regimen were informative and merited early publication.

MATERIALS AND METHODS

Patients aged 18 years and older with biopsy-proven MN were eligible to participate in this study. Patients were required to have persistent nephrotic-range proteinuria (>3.5 g/d proteinuria) after a minimum observation phase of 6 months and at least 2 months of treatment with renin–angiotensin system blockade. Presence of PLA_2R autoantibody in serum or in glomerular deposits was not required for inclusion. Exclusion criteria included estimated glomerular filtration rate (eGFR) <40 ml/min per 1.73 m^2 (determined by the 2009 CKD-EPI creatinine equation[25]), prior treatment with CNI for ≥6 months, any previous treatment with rituximab, pregnancy, nursing mothers, or subjects not practicing birth control. Patients with an active infection, diabetes, or a likely secondary cause of MN were excluded. The NIDDK Institutional Review Board approved the protocol. All participants provided informed consent as per the Declaration of Helsinki for Medical Research Involving Human Subjects. The study was performed at the NIH Clinical Center in Bethesda, Maryland. Rituximab was provided by Genentech through its Investigator Sponsored Trials program. Genentech did not participate in study design, data collection, or analysis or writing of the report.

Run-in Period

Potential participants were managed with standard supportive therapy for a minimum of 6 months prior to study enrollment ("observation phase") in order to assess for spontaneous recovery. During this phase, they received a regimen of angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), or both, along with adjunctive antihypertensives if necessary to achieve target systolic blood pressure of <130 mm Hg, statins for control of lipids, dietary sodium restriction, and loop diuretics to control edema. Patients were eligible for enrollment in the treatment trial after the observation phase if they had persistent nephrotic-range proteinuria that did not show evidence of decline from baseline. Earlier initiation of immunosuppression was allowed if the patient suffered from a significant complication of the NS, such as a thrombotic event.

Immunosuppressive Regimen

Experimental treatment consisted of "induction" with rituximab plus oral cyclosporine followed by "maintenance" rituximab. Both cyclosporine and rituximab were initiated on day 1 of the formal trial period. Cyclosporine (Gengraf) was initiated at a dose of 3 mg/kg/d, given in divided equal doses at 12-hour intervals. The dose was adjusted according to 12-hour trough blood concentrations to achieve a concentration of 125 to 190 μg/l and to avoid toxicity. The first cycle of rituximab was given at a dose of 1000 mg i.v. on day 1 and day 15. After 6 months of therapy during the