important factors such as patient satisfaction and quality of life must be considered in the choice of dialysis treatment. Studies have shown that PD patients have more satisfaction with their overall care compared with HD patients, and that quality of life is better in some domains for PD patients and better in other domains for HD patients.[18,19] Since there is no conclusive evidence that either PD or HD provide any specific survival advantage, patients should be informed about the above specific tradeoffs and actively participate as early as possible in the decision-making process regarding their choice of dialysis modality.

DISCLOSURES

None.

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See related article, "Selection Bias Explains Apparent Differential Mortality Between Dialysis Modalities," on pages 1534–1542.

Circulating Anti-PLA$_2$R Autoantibodies to Monitor Immunological Activity in Membranous Nephropathy

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Experimental and human data converge to indicate that deposition along the glomerular basement membrane of immunoglob-

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ulins produced by autoreactive B cells may initiate a sequence of events resulting in complement activation,[1] impaired sieving function of the glomerular capillary wall and the pore-forming slit diaphragm,[2] and eventual proteinuria that characterizes idiopathic membranous nephropathy (IMN).[3] Thus, treatment with agents that selectively inhibit the production of nephritogenic antibodies would likely be the most effective intervention to prevent one of the earliest steps in the sequence of pathogenic events underlying progressive renal dysfunction in IMN.

Until the early nineties, however, no specific anti-B cell therapies were available and therapeutic approaches to IMN mostly relied on steroids and cytotoxics with or without calcineurin inhibitors. Such agents have significant nonspecific toxicity. On the other hand, kidney survival in patients who do not undergo spontaneous remission[4] has not been substantially improved over the last 30 yr, to the extent that as many as 40% of patients with IMN still progress to end-stage kidney disease despite treatment.[5]

Rituximab, a monoclonal antibody against the CD20 antigen present on B cells, was approved by the Food and Drug Administration in 1997 for the treatment of relapsing or refractory non-Hodgkin's lymphoma and, more recently, for patients with rheumatoid arthritis.[6] Since the CD20 antigen is not expressed on hematopoietic stem cells, normal plasma cells or other normal tissues, selective B cell depletion by rituximab therapy soon surfaced as a potential, specific therapeutic option for IMN.

With this background, rituximab was initially tested in a small cohort of eight IMN patients with severe nephrotic syndrome unresponsive to prolonged angiotensin converting enzyme (ACE) inhibitor therapy.[7] Rituximab infusion was well tolerated and led to a significant reduction in proteinuria and amelioration of nephrotic syndrome in all of the cases. The effect was sustained over one year of follow-up and was associated with a reduction in body weight, diastolic BP, and serum cholesterol.[8] Since this initial experience, other groups have consistently reported the efficacy of rituximab in reducing proteinuria in patients with IMN and nephrotic syndrome.[9,10] In confirmation of the superior effectiveness of interventions targeted to specific pathogenetic mechanisms compared with nonspecific immunosuppression, when used as second-line treatment, rituximab safely and persistently reduced proteinuria in IMN patients who had previously failed to respond to steroids, alkylating agents, or calcineurin inhibitors, or who had relapsed after transient remission.[11,12]

Finding that selective B cell depletion lowered proteinuria in patients with IMN points to a pathogenetic role of antibody-producing lymphocytes in this disease. While renal antigens have been elusive until recently, in 2002, neutral endopeptidase (NEP) was identified as the target antigen in newborns with NEP-deficient mothers, providing evidence for the notion that a human podocyte antigen could serve as a target for nephritogenic antibodies.[13] More recently, antibodies against cationic bovine serum albumin have been implicated in pediatric cases of IMN.[14] Finally, M-type phospholipase A2 receptor (PLA_2R) has been shown as the first podocyte antigen involved in IMN in adults.[15] Detection of these autoantibodies might help in differentiating primary from secondary forms of the disease and monitoring responses to treatment.

In this issue of *JASN*, Beck *et al.* evaluated the relationship between changes in serum anti-PLA_2R autoantibody levels and response to rituximab therapy in 35 adult patients with IMN. Circulating autoantibodies were detected in 80% of patients at baseline, and their titers decreased after rituximab therapy in the majority of them.[16] Importantly, reduction of anti-PLA_2R autoantibody levels anticipated the decline of proteinuria and, in one patient with a relapse of proteinuria, the reemergence of the autoantibody in the circulation preceded recurrence of disease.

According to these findings, monitoring anti-PLA_2R autoantibodies might help titrating IMN therapy to the activity level of disease. In patients with declining autoantibody titer despite stable proteinuria, one may choose to wait to see whether a sustained normalization of antibody titer simply precedes a beneficial effect on proteinuria without need for further intervention. Information on the autoantibody titer would also be valuable in selecting patients for clinical trials of immunosuppressive interventions to avoid the inclusion of subjects with less active disease. On the other hand, some degree of residual proteinuria can persist even after prolonged remission of autoimmune response, as a result of chronic glomerular damage induced by the initial immunological insult that progressed independently of the immune process. This is in line with results of a previous report showing that the severity of chronic renal lesions on biopsy predicts the degree of residual proteinuria after rituximab therapy.[17] In these cases, nonimmune nephroprotective strategies targeting the renin angiotensin system should be implemented to maximally reduce proteinuria.

According to the findings by Beck *et al.*, however, approximately one third of patients with IMN might be expected to have a partial proteinuria remission despite persistently high levels of anti-PLA_2R autoantibodies. Similar findings have has been reported in patients with antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, where clinical response is not always associated with ANCA titer decline.[18] This finding also suggests that, in these clinical conditions, autoantibodies other than anti-PLA_2R or antineutrophil cytoplasmic antibodies may be involved in the autoimmune response. On the other hand, it can be speculated that rituximab also reduces the proteinuria of IMN by immune-independent mechanisms. It is also possible that rituximab has a direct action on podocytes, as was recently shown in focal segmental glomerulosclerosis (FSGS), where the antibody appears to target sphingomyelin phosphodiesterase acid-like 3b, preventing the remodeling of the cytoskeleton.[19] It is unlikely, however, that a direct effect on podocyte explains the beneficial effect of rituximab in IMN due to the strong correlation between antibody titer and proteinuria documented in the paper under consideration here.

In analogy with other autoimmune diseases such as thrombotic thrombocytopenic purpura, where dosing of pathogenic anti-ADAMTS 13 autoantibodies in the circulation, in combination with markers of microangiopathic hemolysis, may help to monitor disease activity and guide specific intervention[20] in patients with IMN, combined assessment of circulating anti-PLA_2R

autoantibodies and proteinuria may be instrumental in optimizing patient care and hopefully improving long term outcomes.

DISCLOSURES

None.

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See related article, "Rituximab-Induced Depletion of Anti-PLA_2R Autoantibodies Predicts Response in Membranous Nephropathy," on pages 1543–1550.