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.

REFERENCES

1. Korevaar JC, Feith GW, Dekker FW, van Manen JG, Boeschoten EW, Bossuyt PM, Krediet RT: NECOSAD Study Group: Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. NECOSAD Study Group. *Kidney Int* 64: 2222–2228, 2003
2. Bloembergen WE, Port FK, Mauger EA, Wolfe RA: A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 6: 177–183, 1995
3. Collins AJ, Hao W, Xia H, Ebben JP, Everson SE, Constantini EG, Ma JZ: Mortality risks of peritoneal dialysis and hemodialysis. *Am J Kidney Dis* 34: 1065–1074, 1999
4. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E: Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 171: 110–118, 2011
5. Termorshuizen F, Korevaar JC, Dekker FW, Van Manen JG, Boeschoten EW, Krediet RT: Hemodialysis and peritoneal dialysis: Comparison of adjusted mortality rates according to the duration of dialysis: Analysis of The Netherlands Cooperative Study on the Adequacy of Dialysis 2. The Netherlands Cooperative Study on the Adequacy of Dialysis Study Group. *J Am Soc Nephrol* 14: 2851–2860, 2003
6. Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS, Levin NW, Sadler JH, Kliger A, Powe NR: Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 143: 174–183, 2005
7. Tanna MM, Vonesh EF, Korbet SM: Patient survival among incident peritoneal dialysis and hemodialysis patients in an urban setting. *Am J Kidney Dis* 36: 1175–1182, 2000
8. Foley RN, Parfrey PS, Harnett JD, Kent GM, O'Dea R, Murray DC, Barre PE: Mode of dialysis therapy and mortality in end-stage renal disease. *J Am Soc Nephrol* 9: 267–276, 1998
9. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, Powe NR: The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 137: 479–486, 2002
10. Astor BC, Eustace JA, Powe NR, Klag MJ, Sadler JH, Fink NE, Coresh J: Timing of nephrologist referral and arteriovenous access use: The CHOICE Study. *Am J Kidney Dis* 38: 494–501, 2001
11. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W: Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int* 55: 1081–1090, 1999
12. Quinn RR, Hux JE, Oliver MJ, Austin PC, Tonelli M, Laupacis A: Selection bias explains apparent differential mortality between dialysis modalities. *J Am Soc Nephrol* 22: 1534–1542, 2011
13. Inrig JK, Sun JL, Yang Q, Briley LP, Szczech LA: Mortality by dialysis modality among patients who have end-stage renal disease and are awaiting renal transplantation. *Clin J Am Soc Nephrol* 1: 774–779, 2006
14. Couchoud C, Moranne O, Frimat L, Labeeuw M, Allot V, Stengel B: Associations between comorbidities, treatment choice and outcome in the elderly with end-stage renal disease. *Nephrol Dial Transplant* 22: 3246–3254, 2007
15. Perl J, Wald R, McFarlane P, Bargman JM, Vonesh E, Na Y, Jassal SV, Moist L: Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol* 22: 1113–1121, 2011
16. Jaar BG, Plantinga LC, Crews DC, Fink NE, Hebah N, Coresh J, Kliger AS, Powe NR: Timing, causes, predictors and prognosis of switching from peritoneal dialysis to hemodialysis: A prospective study. *BMC Nephrol* 10: 3, 2009
17. Mujais S, Story K: Peritoneal dialysis in the US: Evaluation of outcomes in contemporary cohorts. *Kidney Int Suppl* 70: S21–S26, 2006
18. Rubin HR, Fink NE, Plantinga LC, Sadler JH, Kliger AS, Powe NR: Patient ratings of dialysis care with peritoneal dialysis vs hemodialysis. *JAMA* 291: 697–703, 2004
19. Wu AW, Fink NE, Marsh-Manzi JV, Myer KB, Finkelstein FO, Chapman MM, Powe NR: Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *J Am Soc Nephrol* 15: 743–753, 2004

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

Circulating Anti-PLA_2R Autoantibodies to Monitor Immunological Activity in Membranous Nephropathy

Paolo Cravedi, Piero Ruggenenti, and Giuseppe Remuzzi

Mario Negri Institute for Pharmacological Research, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso and Unit of Nephrology and Dialysis, Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy

J Am Soc Nephrol 22: 1400–1402, 2011.
doi: 10.1681/ASN.2011060610

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

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Giuseppe Remuzzi, Mario Negri Institute for Pharmacological Research, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Via Stezzano, 87, 24126 Bergamo, Italy. Phone: +39-035-42131; Fax: +39-035-319-331; E-mail: giuseppe.remuzzi@marionegri.it

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.

REFERENCES

1. Sacks S, Zhou W: New boundaries for complement in renal disease. *J Am Soc Nephrol* 19: 1865–1869, 2008
2. Gagliardini E, Conti S, Benigni A, Remuzzi G, Remuzzi A: Imaging of the porous ultrastructure of the glomerular epithelial filtration slit. *J Am Soc Nephrol* 21: 2081–2089, 2010
3. Ronco P, Debiec H: Antigen identification in membranous nephropathy moves toward targeted monitoring and new therapy. *J Am Soc Nephrol* 21: 564–569, 2010
4. Polanco N, Gutierrez E, Covarsi A, Ariza F, Carreno A, Vigil A, Baltar J, Fernandez-Fresnedo G, Martin C, Pons S, Lorenzo D, Bernis C, Arrizabalaga P, Fernandez-Juarez G, Barrio V, Sierra M, Castellanos I, Espinosa M, Rivera F, Oliet A, Fernandez-Vega F, Praga M: Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 21: 697–704, 2010
5. Ruggenenti P, Cravedi P, Remuzzi G: Latest treatment strategies for membranous nephropathy. *Expert Opin Pharmacother* 8: 3159–3171, 2007
6. Taylor RP, Lindorfer MA: Immunotherapeutic mechanisms of anti-CD20 monoclonal antibodies. *Curr Opin Immunol* 20: 444–449, 2008
7. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P: Rituximab for idiopathic membranous nephropathy. *Lancet* 360: 923–924, 2002
8. Ruggenenti P, Chiurchiu C, Brusegan V, Abbate M, Perna A, Filippi C, Remuzzi G: Rituximab in idiopathic membranous nephropathy: A one-year prospective study. *J Am Soc Nephrol* 14: 1851–1857, 2003
9. Bomback AS, Derebail VK, McGregor JG, Kshirsagar AV, Falk RJ, Nachman PH: Rituximab therapy for membranous nephropathy: A systematic review. *Clin J Am Soc Nephrol* 4: 734–744, 2009
10. Fervenza FC, Cosio FG, Erickson SB, Specks U, Herzenberg AM, Dillon JJ, Leung N, Cohen IM, Wochos DN, Bergstralh E, Hladunewich M, Cattran DC: Rituximab treatment of idiopathic membranous nephropathy. *Kidney Int* 73: 117–125, 2008
11. Cravedi P, Sghirlanzoni MC, Marasa M, Salerno A, Remuzzi G, Ruggenenti P: Efficacy and safety of rituximab second-line therapy for membranous nephropathy: A prospective, matched-cohort study. *Am J Nephrol* 33: 461–468, 2011
12. Segarra A, Praga M, Ramos N, Polanco N, Cargol I, Gutierrez-Solis E, Gomez MR, Montoro B, Camps J: Successful treatment of membranous glomerulonephritis with rituximab in calcineurin inhibitor-dependent patients. *Clin J Am Soc Nephrol* 4: 1083–1088, 2009
13. Debiec H, Guigonis V, Mougenot B, Decobert F, Haymann JP, Bensman A, Deschenes G, Ronco PM: Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. *N Engl J Med* 346: 2053–2060, 2002
14. Debiec H, Lefeu F, Kemper MJ, Niaudet P, Deschenes G, Remuzzi G, Ulinski T, Ronco P: Early-childhood membranous nephropathy due to cationic bovine serum albumin. *N Engl J Med* 364: 2101–2110, 2011
15. Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 361: 11–21, 2009
16. Beck LH, Fervenza FC, Beck DM, Bonegio RGB, Malik FA, Erickson SB, Cosio FG, Cattran DC, Salant DJ: Rituximab-induced depletion of anti-PLA_2R autoantibodies predicts response in membranous nephropathy. *J Am Soc Nephrol* 22: 1543–1550, 2011
17. Ruggenenti P, Chiurchiu C, Abbate M, Perna A, Cravedi P, Bontempelli M, Remuzzi G: Rituximab for idiopathic membranous nephropathy: who can benefit? *Clin J Am Soc Nephrol* 1: 738–748, 2006
18. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363: 221–232, 2010
19. Fornoni A, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, Li J, Mattiazzi A, Ciancio G, Chen L, Zilleruelo G, Abitbol C, Chandar J, Seeherunvong W, Ricordi C, Ikehata M, Rastaldi MP, Reiser J, Burke GW 3rd: Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 3: 85ra46, 2011
20. Bresin E, Gastoldi S, Daina E, Belotti D, Pogliani E, Perseghin P, Scalzulli PR, Paolini R, Marceno R, Remuzzi G, Galbusera M: Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. *Thromb Haemost* 101: 233–238, 2009

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