Antiphospholipase A2 Receptor Autoantibody Guided Diagnosis and Treatment of Membranous Nephropathy: A New Personalized Medical Approach

Richard J. Glassock

Clin J Am Soc Nephrol 9: 1341–1343, 2014. doi: 10.2215/CJN.05880614

Department of Medicine, Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California

Correspondence: Dr. Richard J. Glassock, 8 Bethany, Laguna Niguel, CA 92677. Email: glassock@cox.net

Medical care is entering into a new phase of "personalized" medical care in which diagnosis and management are tailored to the specific aspects of individual patients. This approach is often guided by the results of sophisticated biomarkers of disease, prognosis, or treatment responsiveness. In this issue of *CJASN*, Bech and coworkers from the Radboud University Medical Center (Nijmegen, The Netherlands) and Manchester Institute of Nephrology (Manchester, UK) describe their findings from an observational, prospective study of the clinical utility of measurement of antiphospholipase A2 receptor autoantibody (aPLA2R) in a cohort of patients with presumed primary (idiopathic) membranous nephropathy (iMN) and nephrotic syndrome (1). This study builds on the now well known and ground-breaking studies that defined a pathogenic role of such autoantibodies in iMN, described by Beck *et al.* in 2009 (2).

This new study is particularly timely because the US Food and Drug Administration recently approved the commercial sale of assays (indirect immunofluorescence assay [IFA] and ELISA, Euroimmun, Morris Plains, NJ) for circulating aPLA2R on May 29 and June 27, 2014 (3). Similar assays have previously been approved for use in Europe. Thus, the stakes for resolving uncertainties regarding application of measurements of aPLA2R in iMN have escalated considerably, and the pace of investigation in this arena of disease serology has dramatically quickened. Because of the novelty of this emerging area of study, it is not surprising that many questions surround the precise role of such aPLA2R measurements in patients with nephrotic syndrome in general and specifically in those with membranous nephropathy (MN), either idiopathic or secondary.

Two authors of the current study have recently outlined the general nature of these uncertainties (4): (*1*) Which assay for aPLA2R is best? (*2*) Can an aPLA2R measurement be used to diagnose iMN without resort to renal biopsy? (*3*) Can an aPLA2R assay accurately separate iMN from secondary forms of MN? (*4*) Can quantification of aPLA2R predict outcome or guide the treatment of iMN? In addition, they address the potential value of combining aPLA2R measures and PLA2R antigen staining of renal biopsy specimens in the diagnosis of iMN. For the sake of completeness, another poorly understood issue that needs mention and much further study is the role of aPLA2R measurements in assessing the risk and the course of recurrence of iMN in renal allografts.

Bech and colleagues' study was sharply focused on the utility of pre- and post-treatment assays of aPLA2R on short- and long-term outcomes (mainly remissions and relapses of proteinuria during and after treatment with alkylating agents [cyclophosphamide], mycophenolate mofetil [MMF], or rituximab) in iMN. It is noteworthy that none of the patients included in this study received calcineurin inhibitors, at least initially, perhaps because of the potential for adverse events in patients with reduced renal function. The study size was relatively small (48 patients), and most of the study sample consisted of "high-risk" patients with impaired renal function and/or high-grade proteinuria and severe nephrotic syndrome. Whether the results apply equally to patients with milder disease is unknown. However, the prolonged follow-up (up to 5 years) was a real strength of the study. An ELISA was used to quantify aPLA2R, so the relevance of these findings to results from the IFA will need to be confirmed. Although there is generally a high degree of concordance between the ELISA and IFA results for aPLA2R, discordant results can occasionally be observed (5,6).

The key findings of this preliminary but valuable study is that aPLA2R, while commonly found at the discovery of iMN (sensitivity of about 70%), does not reliably predict the initial response to treatment, regardless of the agent used, even though an alkylating agent regimen was more effective than MMF in quickly reducing the aPLA2R levels. As in other studies, the authors confirmed that the aPLA2R levels decline before the development of remissions of proteinuria and that such remissions can develop weeks or months after the discontinuation of treatment (7–9). Perhaps most important, the level of aPLA2R at the end of treatment predicted the long-term outcomes. According to a Kaplan–Meier analysis, about 55% of patients who were PLA2R negative at the completion of therapy remained in remission for 5 years, compared with none in remission at 2 years after completion of treatment in the aPLA2R-positive group (see Figure 2 in Bech and colleagues' paper).

While more hypothesis-generating than definitive, these novel studies, when added to prior investigations, suggest that a new paradigm of a personalized approach to diagnosis and management of MN based on the results of aPLA2R may be emerging.

First, the results of aPLA2R in nephrotic patients indicates the likely finding of iMN on renal biopsy only if the test result is positive, regardless of the assay method. However, some studies have found positivity for aPLA2R in a few patients with MN and concurrent disease, such as lupus, hepatitis B, sarcoidosis, graft-versus-host disease in the setting of allogeneic bone marrow transplantation, or cancer (10–13). It is possible that some of these cases represent iMN superimposed on a coincidental disease. If staining for PLA2R antigen in glomeruli is positive and IgG4 is the dominant immunoglobulin in the deposits, then iMN is more likely than not (14). A positive aPLA2R is very seldom (if ever) seen in patient with non-MN lesion on kidney biopsy.

Second, a high value for the quantification of circulating aPLA2R indicates a lower likelihood of a spontaneous remission (<10%) and therefore might be used as a rationale for immediate therapy in patients with less severe disease (8).

Third, when a patient with clinical and pathobiological features suggestive of iMN (glomerular PLA2R antigen positive and with dominant IgG4 deposits) has a low or negative value for aPLA2R, a delay in initiating treatment might be appropriate because these findings may herald a subsequent partial or complete spontaneous remission. Furthermore, patients who are aPLA2R negative but have persistent proteinuria may have immunologically inactive disease but irreversible damage to the glomerular permeability barrier (15). Alternatively, those who are negative for aPLA2R and have nephrotic syndrome (responsive to therapy) may have disease due to autoantibodies to other non-PLA2R podocyte antigens (16).

Fourth, the level of aPLA2R should probably not be used as a sole criterion for a decision to treat or not to treat, nor should the presence or absence of aPLA2R be used for choosing among the several treatment regimens available for initial treatment of iMN (17).

Fifth, whenever possible, secondary forms of MN should be excluded in aPLA2R-negative patients with MN on renal biopsy, especially if the PLA2R antigen staining of glomeruli is also negative or when IgG deposits are mainly non-IgG4 subclass (18).

Sixth, serial measurement of aPLA2R during (possibly monthly or bimonthly) and at the end of a scheduled treatment regimen should be routine. Although the data are scanty and uncontrolled, I agree with Bech *et al.* that clinicians should consider discontinuing treatment if the aPLA2R result becomes negative after the first 2–3 months of treatment. In addition, a change in treatment regimen should be considered if aPLA2R positivity persists (most often without a remission) for >6 months after the start of "specific" treatment for iMN.

Finally, as noted by Bech *et al.*, some patients with iMN refractory to treatment with alkylating agents or MMF will continue to be aPLA2R positive without remission as they progress to ESRD. Such patients might be at higher risk for recurrence of iMN in a renal allograft, but the exact magnitude of this risk and the utility of serial PLA2R measurement before and after renal transplantation require further exploration. In addition, we do not yet have complete information on a cohort of patients treated exclusively with calcineurin inhibitors.

Obviously, this field is in a very fluid state. As new data emerge, these preliminary applications of the "new serology" of iMN will likely change. For example, next generation assays for aPLA2R may be more specific for the immunodominant epitope on the PLA2R antigen. Nevertheless, it is now firmly and unequivocally established that most cases of iMN are due to an ongoing autoimmune process regulated by underlying genetic predisposing factors at the human leukocyte antigen locus on chromosome 6 and by single-nucleotide polymorphisms at the PLA2R locus on chromosome 2 (19), but we are still largely ignorant of etiologic factors involved in iMN. The knowledge of pathogenesis we do possess and the new "artillery" of aPLA2R serology, as examined by Bech *et al.*, offer great promise to eventually lead to a highly individualized approach to diagnosis, prognosis, and management of MN, not the "one size fits all" strategy often exemplified in current clinical practice guidelines.

Disclosures

R.J.G. is a compensated consultant to Genentech, Questcor, Novartis, Astellas, Eli Lilly, Bristol-Myers Squibb, Abbvie, Sanofi-Genzyme, and Mitusbishi-Tanabe, all of whom sell products used in treatment of membranous nephropathy or have investigational products in development. He is also on the speakers bureau for Genentech andis a compensated editor for UpToDate.

References

1. Bech AP, Hofstra JM, Brenchley PE, Wetzels JFM: Association of anti-PLA2R-antibodies with outcomes after immunosuppressive therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol*. 9: 1386–1392, 2014
2. 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
3. Euroimmun US: FDA allows marketing of first non-invasive test to help in identifying cause of certain kidney disease. May 29, 2014. Available at http://www.euroimmun.us/fda-released/new-fda-release-pla2r-ifa. US Food and Drug Administration http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K132195. Both Accessed June 27, 2014
4. Hofstra JM, Wetzels JFM: Phospholipase A2 receptor antibodies in membranous nephropathy: Unresolved issues. *J Am Soc Nephrol* 25: 1137–1139, 2014
5. Dähnrich C, Komorowski L, Probst C, Seitz-Polski B, Esnault V, Wetzels JF, Hofstra JM, Hoxha E, Stahl RA, Lambeau G, Stöcker W, Schlumberger W: Development of a standardized ELISA for the determination of autoantibodies against human M-type phospholipase A2 receptor in primary membranous nephropathy. *Clin Chim Acta* 421: 213–218, 2013
6. Hofstra JM, Debiec H, Short CD, Pellé T, Kleta R, Mathieson PW, Ronco P, Brenchley PE, Wetzels JF: Antiphospholipase A2 receptor antibody titer and subclass in idiopathic membranous nephropathy. *J Am Soc Nephrol* 23: 1735–1743, 2012
7. Hoxha E, Thiele I, Zahner G, Panzer U, Harendza S, Stahl RA: Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. *J Am Soc Nephrol* 25: 1357–1366, 2014
8. Hofstra JM, Beck LH Jr, Beck DM, Wetzels JF, Salant DJ: Anti-phospholipase A_2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 6: 1286–1291, 2011
9. Beck LH Jr, Fervenza FC, Beck DM, Bonegio RG, Malik FA, Erickson SB, Cosio FG, Cattran DC, Salant DJ: Rituximab-induced depletion of anti-PLA2R autoantibodies predicts

response in membranous nephropathy. *J Am Soc Nephrol* 22: 1543–1550, 2011
10. Qin W, Beck LH Jr, Zeng C, Chen Z, Li S, Zuo K, Salant DJ, Liu Z: Anti-phospholipase A2 receptor antibody in membranous nephropathy. *J Am Soc Nephrol* 22: 1137–1143, 2011
11. Gunnarsson I, Schlumberger W, Rönnelid J: Antibodies to M-type phospholipase A2 receptor (PLA2R) and membranous lupus nephritis. *Am J Kidney Dis* 59: 585–586, 2012
12. Knehtl M1, Debiec H, Kamgang P, Callard P, Cadranel J, Ronco P, Boffa JJ: A case of phospholipase A2 receptor-positive membranous nephropathy preceding sarcoid-associated granulomatous tubulointerstitial nephritis. *Am J Kidney Dis* 57: 140–143, 2011
13. Kanigicherla D, Gummadova J, McKenzie EA, Roberts SA, Harris S, Nikam M, Poulton K, McWilliam L, Short CD, Venning M, Brenchley PE: Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. *Kidney Int* 83: 940–948, 2013
14. Qu Z, Liu G, Li J, Wu LH, Tan Y, Zheng X, Ao J, Zhao MH: Absence of glomerular IgG4 deposition in patients with membranous nephropathy may indicate malignancy. *Nephrol Dial Transplant* 27: 1931–1937, 2012
15. Fervenza FC, Glassock RJ, Bleyer AJ: American Society of Nephrology Quiz and Questionnaire 2012: glomerulonephritis. *Clin J Am Soc Nephrol* 8: 1460–1465, 2013
16. Murtas C, Bruschi M, Candiano G, Moroni G, Magistroni R, Magnano A, Bruno F, Radice A, Furci L, Argentiero L, Carnevali ML, Messa P, Scolari F, Sinico RA, Gesualdo L, Fervenza FC, Allegri L, Ravani P, Ghiggeri GM: Coexistence of different circulating anti-podocyte antibodies in membranous nephropathy. *Clin J Am Soc Nephrol* 7: 1394–1400, 2012
17. KDIGO clinical practice guidelines for glomerulonephritis *Kidney Int Suppl* 2: 186–197, 2012
18. Svobodova B, Honsova E, Ronco P, Tesar V, Debiec H: Kidney biopsy is a sensitive tool for retrospective diagnosis of PLA2R-related membranous nephropathy. *Nephrol Dial Transplant* 28: 1839–1844, 2013
19. Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, Voinescu C, Patel N, Pearce K, Hubank M, Stephens HA, Laundy V, Padmanabhan S, Zawadzka A, Hofstra JM, Coenen MJ, den Heijer M, Kiemeney LA, Bacq-Daian D, Stengel B, Powis SH, Brenchley P, Feehally J, Rees AJ, Debiec H, Wetzels JF, Ronco P, Mathieson PW, Kleta R: Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 364: 616–626, 2011

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

See related article, "Association of Anti-PLA_2R Antibodies with Outcomes after Immunosuppressive Therapy in Idiopathic Membranous Nephropathy," on pages 1386–1392.