

**Antibodies to M-type phospholipase receptor and immunological remission in treatment resistant and relapsing membranous nephropathy**

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Sir,

The report by Van de Logt and colleagues adds to the expanding literature on the utility of measurement of antibodies against M-type phospholipase A2 receptor (aPLA2R) diverse clinical circumstances in management of patients with membranous nephropathy.<sup>1</sup> They show that rituximab is less effective than cyclophosphamide in effecting reduction in aPLA2R levels (immunological response), and that baseline antibody titers predict response to treatment, whether with rituximab or cyclophosphamide. The literature is scarce on antibody measurement in those with treatment resistant or relapsing disease.

Here we report on the kinetics of aPLA2R during 35 episodes of refractory/ relapsing membranous nephropathy treated with various regimes in 33 patients. Antibody levels were measured prior to commencement of the rescue therapy for treatment resistant or relapse following the initial therapy and 6 months after completion of rescue therapy. The mean age of the patients was  $40.08 \pm 14.36$  years, and the duration of the disease was  $23.34 \pm 10.47$  months. The treatment regimens were cyclical cyclophosphamide/ steroids (cCTX/GC), tacrolimus (TAC) and rituximab in 12, 07 and 16 patients, respectively. A total of 15 (42.85%) patients achieved immunological remission (aPLA2R <14 RU/mL). Patients on TAC, cCTX/GC and rituximab, had a median 9.08 (-20.22,41.34), 99.10 (76.01,99.74), 86.48 (65.72,96.05) percentage point reduction in aPLA2R levels. Patients treated with cCTX/GC or rituximab had a significant reduction ( $p < 0.001$ ) in aPLA2R titer, whereas no significant decline was apparent in the TAC group (Supplemental Figure 1). We divided patients into tertiles based on pre-treatment antibody levels.<sup>2</sup> Patients in the 3rd tertile responded poorly to therapy (Figure 1). Details of individual patients, including details of the initial treatment, are mentioned in Supplementary Table 1.

This report documents the utility of anti-PLA2R levels in predicting response to treatment in relapsing or resistant membranous nephropathy. Eighty five percent of the patients treated with TAC rescue failed to achieve serological remission. Although the number of cases is small, poor immunological response could be the potential reason why most of the patients relapse on stopping TAC, when the functional effect of the drug is lost. We also show that rituximab can induce immunological remission in a significant proportion of patients who were either resistant to or have relapsed following CTX/GC therapy. Small sample size limits our conclusion on the efficacy of cCTX/GC rescue in rituximab resistant/ relapsing cases.

## References:

1. van de Logt AE, Dahan K, Rousseau A, van der Molen R, Debiec H, Ronco P, Wetzels J. Immunological remission in PLA2R-antibody-associated membranous nephropathy: cyclophosphamide versus rituximab. *Kidney Int.* 2018;93(4):1016-1017.
2. Ramachandran R, Kumar V, Kumar A, Yadav AK, Nada R, Kumar H, et al. PLA2R antibodies, glomerular PLA2R deposits and variations in PLA2R1 and HLA-DQA1 genes in primary membranous nephropathy in South Asians. *Nephrol Dial Transplant.* 2016;31(9):1486-93.

**Figure legend:**

Fig 1: Proportion of episodes responding to treatment in various aPLA2R tertiles

Supplementary Fig 1: Pre and post-treatment aPLA2R levels.