Do circulating antibodies against C1q reflect the activity of lupus nephritis?

Letter to the Editor I read with interest the study on anti-C1q antibodies (anti-C1q Abs) for disease activity in lupus nephritis.[1] According to the study, anti-C1q were positive in nearly 80% of the subjects with active lupus nephritis vs. around 30% of those with inactive lupus nephritis, which is in line with the existing studies.[2-4] However, in the active group, sampling for anti-C1q Abs was done much later in 16 patients than the renal biopsy (on average, 5 months elapsed). Were these patients truly a representation of active nephritis or were they in fact refractory nephritis, which was nonresponsive to the standard treatment? And it is unclear as to whether the patients received adequate treatment for nephritis, with the authors stating that only 18% had received cyclophosphamide previously, which would be undertreatment as per current guidelines at least for class III and IV nephritis.[5]

It has been shown previously that C1q may be a marker of disease response. A study by Cai t al. found better remissions in those whose anti-C1q Abs decreased by 50% or more.[6] Does the positive C1q in patients, who were biopsied some time before the sampling and presumably undertreated, represent C1q as a marker of poor response rather than purely activity in this case? It will be interesting to find out what happened to anti-C1q Abs in another group of patients of treated lupus nephritis, who after 5 to 6 months had low disease activity, and this may be a more comparable group than the 16 patients who had poor response to treatment.

Correspondence to: Varun Dhir, MD, DM, Chandigarh, India, Post Graduate Institute of Medical Education, e-mail: varundhir@gmail.com.

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Author response Dear Sir, thank you for your interest in the results of our study. Your main concern regards 16 patients assessed as having active lupus nephritis (LN), in whom sampling for anti-C1q antibodies (anti-C1q Abs) was performed 1 to 12 months after biopsy, and thus, they could be considered as having refractory LN. In this subgroup of patients, the mean time between our study and the diagnosis of systemic lupus erythematosus (SLE) was 60 ±22 months. Sixty-two percent of the patients were previously treated with methylprednisolone (MP) intravenously, 31.3% with cyclophosphamide (CYC; 4 of them received maximal doses of CYC before our study), 19% with azathioprine, 6% with antimalarial drugs, and all of them received corticosteroids orally. Among them, 1 patient had class II, 6 had class III, and 9 patients had class IV of LN. The anti-C1q Abs were assessed: in the patient with class II 1 month after biopsy, in patients with class III 1 month (4 cases), 3 months (1 case), and 4 months (1 case) after biopsy, and in those with class IV 1 month (2 cases), 2 months (1 case), 6 months (1 case), 9 months (1 case), and 12 months (4 cases) after biopsy. Regardless of the class of morphological lesions reported earlier in the kidney, the levels of anti-C1q Abs 1, 2, 3, 4, 6, 9, and 12 months after biopsy were 166.2 ±37.3, 100.9, 55.27, 200.09, 660.4, 169.9, and 177.7 ±113.1 U/ml, respectively.[1] In our opinion, such high levels of anti-C1q Abs at these different time points of follow-up were caused by infections that could contribute to the exacerbations of LN in our patients. In this context, during the sampling for anti-C1q Abs, septicemia developed in 1 patient (due to necrotizing fasciitis), bacterial pneumonia in the other 2, active viral infections

in 8 (cytomegalovirus, Epstein-Barr virus, herpes simplex virus), and symptomatic urinary tract infections in 2. These were also contraindications against the use of CYC. In the other 2 patients, such a contraindication was chronic tonsillitis (in one of them associated with newly diagnosed cholecystitis, which had to be operated).

We agree with the results of the recent studies suggesting that monitoring of anti-C1q Abs levels is more useful in clinical practice than their single measurement in sera of patients with SLE. The rising levels of antibodies can precede renal exacerbation of 2 to 6 months and decreasing levels indicate effective treatment.[2-6]

However, in contrast to the findings of Cai et al.,[3] who found the highest levels of anti-C1q Abs in patients with class IV and III,[3] we did not observe the differences in the mean levels between the classes of LN. We also compared these 16 patients with active LN and anti-C1q Abs estimated 1 to 12 months after biopsy with the others, who 5 to 6 months after biopsy were in inactive phase of LN. We found significant differences in the prevalence of increased anti-C1q (87.5% vs. 40%, P <0.05), antibodies against double-stranded DNA (anti-dsDNA) (93.8% vs. 50%, P <0.05), circulating immune complexes binding C1q (62.5% vs. 10%, P <0.05) and decreased levels of complement components C3 (87.5% vs. 10%; P <0.0005) and C4 (75% vs. 0%, P <0.0005). In active LN, the mean levels of anti-C1q Abs were higher than in inactive LN (191.3 ±44.0 vs. 61.6 ±32.6, P <0.05). The same was true for anti-dsDNA (479.4 ±85.3 vs. 78.8 ±11.7, P <0.0005) and lower levels of C3 (0.6 ±0.06 vs. 1.2 ±0.09, P <0.0001) and C4 (0.09 ±0.01 vs. 0.23 ±0.27, P <0.0005).

Cai et al.[3] observed that the concentration of anti-C1q Abs after immunosuppressive therapy is more important than that before the treatment. Persistent high levels of these antibodies may suggest resistance to therapy.[3] Although we have not mentioned this in our original paper, our study showed that bacterial and viral infections are an essential problem in patients with LN, which is in agreement with the analysis of long-term mortality and renal outcome in patients with LN performed by Faurschou et al.[7] Additionally, compared to the study of Moura et al.,[5] who examined the changes in anti-C1q Abs levels in patients with newly diagnosed SLE without any previous treatment, our group of patients was not homogenous. The majority of them where diagnosed few years ago, previously received different type of treatment, and were administered MP orally during examination. This may be the reason why it is impossible to conclude from our study about the role of anti-C1q Abs as a marker of disease response.

Correspondence to: Prof. Zofia I. Niemir, MD, PhD, Laboratory for Molecular Nephrology, Department of Nephrology, Transplantology and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland e-mail: zniemir@ump.edu.pl.

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