

## Dr. Vlachoyiannopoulos replies

To the Editor:

Dr. Korkmaz raises the following issues: (1) the fluctuation of the aCL antibody titers, either spontaneous or modified by prednisone treatment, might be responsible for the upregulation of aPL antibodies after CYC treatment and not CYC itself; (2) his personal experience from 4 patients with SLE treated either with CYC or AZA alone or with prednisone is opposite to our own<sup>1</sup>; (3) the diagnosis of some patients with APS may not be accurate; and (4) renal biopsy findings of a patient with APS nephropathy are missing.

Fluctuation of aCL antibody titers was observed in both treatment groups. However, high antibody titers (absorbance higher than the 99th percentile of 100 normal individuals in ELISA) obtained on 2 occasions 12 weeks apart were commonly detected in the CYC-treated group and constituted the criterion for seroconversion. Patients with high aCL titers tended to be permanently positive for aCL. The patients from both groups were evaluated for aCL antibodies with the same frequency over time. The reports<sup>2,3</sup> suggested by Korkmaz describe sequential measurements of aCL titers and lupus anticoagulant (LAC) in 54 patients with SLE; the design of these studies is not clear, but the non-distinct time intervals of blood sampling and the number of blood samples per patient give the impression that they were retrospective, thus not offering more information than our own study. Our work involved 320 consecutive patients with a mean disease duration of nearly 120 months. Nevertheless, the important knowledge offered by the studies mentioned was taken into account, as follows: first, during SLE remission IgG aCL are present and significantly associated with APS<sup>2</sup>, as we have shown; second, aPL-positive patients with SLE cannot be classified based on only one measurement<sup>3</sup>, as we also emphasize in the definition of seroconversion.

Contribution of Korkmaz's personal experience from 4 patients is welcome. Interestingly, the patient who received only AZA continued to be positive for aPL, while the remaining 3 patients receiving CYC or AZ plus prednisone became negative. It has been suggested that CYC and prednisone do not regulate different antibody specificities in the same way<sup>4</sup>. Regarding aPL responses in particular, lowering of serum titers<sup>5</sup> or no response<sup>6</sup> by prednisone has been suggested. We would point out, however, that an observation based on 4 patient-years as described by Korkmaz is rather weak to draw definite conclusions, compared to our observation, which was based on a sample of more than 3200 patient-years<sup>1</sup>. Ideally, randomized, prospective trials would be necessary to clarify whether CYC downregulates or upregulates aPL responses. Nonetheless, our study is interesting because it is based on strict definitions, large sample size, and appropriate statistical techniques, and finally, promotes interest for randomized trials to definitely clarify the questions raised in this article.

One of the patients with myocardial infarction was diagnosed by electrocardiographic assessment along with abnormal myocardial enzyme kinetics, and the other with coronary catheterization.

We do not administer CYC in patients with SLE nephritis without previous renal biopsy. The case indicated by Korkmaz was a man who presented in 1993 with a 3-month history of ankle edema. He was positive for antinuclear antibodies at a titer of 1/2560 with a fine speckled pattern and anti-U1RNP antibodies. The anti-dsDNA and aCL antibodies were negative. Active urine sediment was detected, while a 24-h urine sample contained 6.5 g protein. Kidney biopsy showed diffuse, proliferative lupus glomerulonephritis with an activity index of 6. Prednisone 1 mg per kg body weight plus CYC pulses were instituted. From 1994 to 1996 the 24-h urine protein fell to 670 mg, but increased again to 1.6 g in July 1996. The patient remained negative for anti-dsDNA antibodies, while the aCL appeared for the first time. Aspirin 100 mg per day was prescribed. In September 1996, February 1999, and September 2001, 3 additional kidney biopsies were performed in order to understand the patients' failure to respond to CYC pulse therapy. This therapy was unsuccessfully changed to a combination of 50 mg CYC and 50 mg AZA in September 2000 and further substituted by mycophenolate mofetil 2 g daily in February 2001, with-

out response. The last 3 biopsies showed: SLE glomerulonephritis WHO class IIIa (activity index 3, chronicity index 0), WHO class IIa (activity index 3, chronicity index 3), and a sclerotic-hyperplastic glomerulonephritis WHO class IVc (activity index 1, chronicity index 6), respectively. Fibrin microthrombi, fibrous intimal hyperplasia, and focal cortical atrophy, all characterizing the APS nephropathy<sup>7</sup>, were also detected in the last biopsy. Therapy was decreased to prednisone 5 mg orally, AZA 150 mg orally, and aspirin 100 mg orally only. The patient later reached endstage renal disease and in December 2002 underwent renal transplantation. Based on high titers of aCL antibodies, as well as recently developed anti- $\beta_2$ -glycoprotein I antibodies, warfarin was also initiated after transplantation, aiming to maintain an international normalized ratio between 2.9 and 3.5.

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