

Do Immunosuppressives Upregulate Antiphospholipid Antibodies?

To the Editor:

I read with great interest the article by Vlachoyiannopoulos, *et al* entitled “Upregulation of antiphospholipid antibodies following cyclophosphamide (CYC) therapy in patients with systemic lupus erythematosus”¹. They report that CYC therapy may result in upregulation of antiphospholipid antibodies (aPL) as well as development of antiphospholipid syndrome (APS) in defiance of suppressed systemic lupus erythematosus (SLE) activity. A few points warrant further explanation by the authors.

While it has been reported that anticardiolipin antibody (aCL) IgG, aCL IgM, and lupus anticoagulant (LAC) may be observed fluctuating during the course of SLE, and LAC may be modified by the treatment with prednisolone^{2,3}, Vlachoyiannopoulos, *et al* have neglected to call attention to this point in their article. Out, *et al* have reported that fluctuations in LAC and aCL IgM antibodies are not associated with disease activity, but that aCL IgG may be associated with disease activity^{2,3}. Out, *et al* have also shown that aCL IgG antibodies may fluctuate during the remission period, whereupon APS may well develop in cases that have never taken CYC. The number of aPL-positive patients is higher in the CYC group than in the non-CYC group, according to the data of Vlachoyiannopoulos, *et al*¹. It is natural to expect an increase in the rate of fluctuations in the CYC group. Therefore, it would not be implausible to speculate that increased titers of aPL antibodies could well have been due to fluctuations of antibodies, rather than due to CYC.

We have prescribed immunosuppressive drugs including CYC and azathioprine (AZA) and low doses of prednisolone for 12 months for 4 of our patients with APS (Table 1)⁴. In 2 of these 4 patients, aCL IgG antibodies changed to negative, while these antibodies continued to stay negative in the remaining 2 patients. As for aCL IgM, it was negative in 2 of the patients at first, but had changed to positive by the end of the 12th month, while it happened the other way round in the other 2 patients. LAC was positive in 3 patients at the beginning of our study. It changed to negative in 2 patients, while it retained its positivity in the remaining 1 patient. While there was improvement in APS nephropathies of all 4 patients, we could not determine homogeneity among the levels of their aCL and LAC antibodies. aCL IgM seroconversion occurred in 2 patients with APS who were taking AZA. Taking all this into consideration, even under immunosuppressive treatments such as CYC and AZA, it is possible to observe fluctuations in levels of aCL and LAC antibodies.

Another point to be raised is how the authors have approached diagnosis of the patients who were said to have developed APS. The authors report that 2 of the patients developed acute myocardial infarction (Patients 1 and 4). They based this diagnosis upon their electrocardiography (ECG) and hemodynamic assessment. However, what exactly they mean by hemodynamic assessment is vague in the article. The changes in ECG may well be secondary to cardiotoxic effects of CYC or coronary vasculitis, which may be seen particularly during the remission period of SLE⁵. Revised criteria of APS have stipulated that an objective criterion should be based upon either an appropriate imaging study or histopathology⁶. Therefore, it would

have been a much better idea to take advantage of coronary angiography or another validated imaging study in order to confirm presence of thrombosis in coronary artery or arteries.

As is well documented, APS nephropathy is a feature associated with APS, although not currently accepted as a criterion for classification of APS⁶. Therefore, it would be assertive to take Case 5 as a real APS case. Since this patient was reported to have had CYC earlier, he is more likely to have lupus nephritis. It would also be useful to know for sure whether renal biopsy had ever been carried out for the patient with APS and its results, if any. Earlier studies have reported that CYC and low doses of steroids may be useful in APS nephropathies⁴. For this reason, it would be interesting to assume that APS may have developed despite CYC and low doses of steroids.

aCL and LAC antibodies may well fluctuate independently from disease activity of SLE. We need more prospective studies to evaluate whether CYC and other immunosuppressive agents may upregulate antiphospholipid antibodies.

CENGİZ KORKMAZ, MD, Professor in Rheumatology, Eskisehir Osmangazi University, Division of Rheumatology, Department of Internal Medicine, Eskisehir, 26480, Turkey. Address reprint requests to Dr. C. Korkmaz, Osmangazi Üniversitesi, Tıp Fakültesi, İç Hastalıkları, Romatoloji Bölümü, 26480, Eskisehir, Türkiye. E-mail: ckorkmaz@ogu.edu.tr

REFERENCES

1. Vlachoyiannopoulos PG, Taya SP, Katsifis G, Zintzaras E, Tzioufas AG, Moutsopoulos HM. Upregulation of antiphospholipid antibodies following cyclophosphamide therapy in patients with systemic lupus erythematosus. *J Rheumatol* 2008;35:1768-75. Epub 2008 Jul 15.

2. Out HJ, de Groot PG, Hasselaar P, van Vliet M, Derksen RH. Fluctuations of anticardiolipin antibody levels in patients with systemic lupus erythematosus: a prospective study. *Ann Rheum Dis* 1989;48:1023-8.

3. Out HJ, van Vliet M, de Groot PG, Hasselaar P, Derksen RH. Prospective study of fluctuations of lupus anticoagulant activity and anticardiolipin antibody titre in patients with systemic lupus erythematosus. *Ann Rheum Dis* 1992;51:353-7.

4. Korkmaz C, Kabukcuoglu S, Isiksoy S, Yalcin AU. Renal involvement in primary antiphospholipid syndrome and its response to immunosuppressive treatment. *Lupus* 2003;12:760-5.

5. Wilson VE, Eck SL, Bates ER. Evaluation and treatment of acute myocardial infarction complicating systemic lupus erythematosus. *Chest* 1992;101:420-4.

6. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.

J Rheumatol 2009;36:2; doi:10.3899/jrheum.080872

Table 1. The changes of antiphospholipid antibody levels under the treatment in patients with antiphospholipid syndrome.

Cases, age/sex	Treatment	aCL IgG/IgM			LAC		
		0 mo	6 mo	12 mo	0 mo	6 mo	12 mo
1. 35/F	CYC + PRD	35/18	1.3/1	8/5	+	ND	–
2. 40/F	AZA + PRD	13/2	6/20	12/18	+	–	–
3. 30/F	AZA	9/7	11/17	7/24	+	+	+
4. 36/F	CYC + PRD	61/42	2/2	20/2	–	ND	–

aCL: anticardiolipin antibody; LAC: lupus anticoagulant; CYC: cyclophosphamide; AZA: azathioprine; PRD: prednisolone; ND: not done. Positivity for aCL IgG > 12 GPL units; for aCL IgM > 11 MPL units.