Table 1 Correlation of anticardiolipin antibodies (aCL) with serological and clinical findings in 50 patients with rheumatoid arthritis. Results are given as number (%) of patients

	aCL+ patients (n=9)	aCL- patients (n=41)	p Value
Age (years)	63.2 +/- 4	63.5 +/- 12	NS
ANA* positive (titre >160)	7 (77)	30 (73)	NS
Sicca syndrome	4 (44)	12 (29)	NS
Extra-articular manifestations	4 (44)	6 (14)	NS
Thrombosis history and/or abortion	1 (11)	3 (7)	NS
Steroid treatment	7 (77)	32 (78)	NS
DMARD* treatment	8 (88)	26 (63)	NS

*ANA = antinuclear antibody; DMARD = disease modifying antirheumatic drug.

satisfying the 1987 American College of Rheumatology criteria for RA. Serum IgG and IgM aCL were characterised by enzyme linked immunosorbent assay (ELISA)¹ using microtitre plates (Immunosorb, Nunc, Roskilde, Denmark) coated with cardiolipin purified from bovine heart (Sigma, St Louis, MO). Wells were saturated with 1% bovine serum albumin (BSA; Diamed, Cressier/Morat, Switzerland) in phosphate buffered saline solution (PBS). Serum samples diluted 1/100 in PBS-BSA were incubated for one hour at 37°C. The blocking and sample diluent buffer did not contain β_2 GP1 and differed from those using fetal calf serum, which are considered to add exogenous β_2 GP1. aCL levels were expressed in IgM and IgG units (U), calculated by including serum samples calibrated with Harris's standards on every plate.² A search was made for IgG and IgM β_2 GP1 antibodies by an ELISA using human β_2 GP1 antigen coated on irradiated plates, according to Arvieux *et al.*³ aCL and β_2 GP1 antibody levels were considered to be positive when greater or equal to 20 U. Rheumatoid factors (RF) (detected by nephelometry) and antinuclear antibodies (ANA) (detected by indirect immunofluorescence (IIF)) were determined for each patient. Additionally, antikeratin antibodies (detected by IIF on sections of rat oesophagus) and the presence of HLA-DR4 or HLA-DR1 were determined for 25 patients. The patients were assessed to determine the presence or absence of extra-articular manifestations of RA and sicca syndrome. A history of arterial or venous thrombosis, recurrent fetal loss, and current treatment—for example, steroid treatment, treatment with disease modifying antirheumatic drugs, and treatment for other diseases, were reviewed. Statistical analysis was performed with the χ^2 test or Fisher's test, as appropriate.

Nine patients (18%) had low titre IgG isotype aCL, but no β_2 GP1 antibodies. There was no correlation with thrombosis or recurrent fetal loss. There was an increase in sicca syndrome and extra-articular manifestations of RA in the aCL+ group, but this was not statistically significant (table 1). No significant association was found between aCL and other autoantibodies (RF, ANA, antikeratin antibodies). No statistically significant association was found between any drug inducing aCL and the presence of aCL. In contrast with our patients, another study found IgG aCL in only 2% of healthy subjects.⁴

β_2 GP1 antibodies were found in 8% of patients with RA, belonging to the IgM class in 75% of these cases. The sera containing IgM β_2 GP1 antibodies also contained positive levels of RF. There was no correlation with any clinical manifestation. β_2 GP1 antibodies were not found in healthy subjects.⁴

The frequency of aCL, all of them β_2 GP1 independent in this study, was close to⁵ or lower than in other studies (39–49%).^{6,7} We found no association with clinical manifestations such as thrombotic events,⁸ or extra-articular manifestations,⁹ or with other autoantibodies (ANA).^{7,9} The relation between IgM β_2 GP1 antibodies and RA remains to be determined; it might be due to non-specific binding with RF.

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Ethical aspects of new medicines targeted at treatment of RA

We read with interest the article reported by Kreutz *et al* "European regulatory aspects on new medicines targeted at treatment of rheumatoid arthritis".¹ The use of placebo studies for the development of new medicines in patients with rheumatoid arthritis (RA) remains controversial.² Placebo studies are useful when testing the effectiveness of new drugs. However, in two studies that compared two active disease modifying drugs with placebo the radiological deterioration was about four times higher in those patients with placebo.^{3,4} In view of this, in 1999 Emery and Smolen suggested that long term placebo studies should be a thing of the past in patients with active RA.⁵ Nowadays, there is enough evidence that single or combined treatments can modify RA. Thus, for example, in a recent prospective and observational study patients with severe RA who responded to methotrexate had a reduced mortality.⁶ Also, in three randomised controlled trials Sharp *et al* demonstrated retardation of radiographic progression by the use of leflunomide.⁷ Observations like these support the possible discontinuation of placebo in studies of active RA. Moreover, patients enrolled in placebo control studies should receive information on the potential risk of permanent and irreversible damage in those receiving placebo without any active disease modifying drug. Finally, at present it is difficult to establish whether six months without any active disease modifying drug in those receiving placebo is acceptable.

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