

## LETTERS TO THE EDITOR

### Cardiac toxicity secondary to long term treatment with chloroquine

Chloroquine is frequently used to treat systemic autoimmune diseases, such as systemic lupus erythematosus (SLE). With long term treatment, associated toxicity is well known, with retinopathy been the most common complication. Other chronic complications include skin disorders (hyperpigmentation), blood dyscrasias, corneal deposits, encephalopathy, neuropathy, myopathy, and impairment of auditory function.<sup>1</sup> Cardiac complications, such as conduction disorders, myocardial hypertrophy, and restrictive cardiomyopathy, have also been reported in long term treatment.<sup>2-10</sup> Nevertheless, this problem is underappreciated. We describe a patient with SLE who developed a complete heart block and a restrictive cardiomyopathy owing to chronic treatment with chloroquine.

#### CASE REPORT

A 64 year old woman was diagnosed with SLE and associated Sjögren's syndrome in 1988. She was treated with chloroquine for seven years (total dose 1000 g). In 1996 she presented a syncope, and a complete heart block was disclosed in the electrocardiogram (ECG), leading to placement of a permanent pacemaker. In April 1997 the patient was admitted into our hospital owing to a biventricular cardiac failure. There were no risk factors for coronary disease. A physical examination showed that the skin was hyperpigmented and she had auditory impairment and proximal limb weakness. Chloroquine retinopathy was found by ophthalmological examination. Biochemistry was normal except for increased hepatic transaminases. Normal results were obtained for ferritin and viral hepatic serological tests. Coronary angiography and pulmonary gammagraphy were normal. A transthoracic ECG was compatible with restrictive myocardialopathy, with a left ventricular ejection fraction of 36%, dilatation of the left auricle, mild mitral insufficiency, and severe tricuspid insufficiency. Hepatic and subcutaneous fat biopsies showed no abnormalities. A myopathic pattern was found on electromyography, and a

muscular biopsy showed isolated muscular fibres and little group atrophy, focal myonecrosis, with little muscular regeneration and the presence of vacuoles, characteristic of chloroquine myopathy. The cardiac symptoms improved significantly with diuretic treatment. Chloroquine was discontinued. Subsequently, the patient has only presented mild, well tolerated biventricular cardiac failure.

Long term chloroquine treatment can produce cardiac complications, such as myocardialopathy, both restrictive and hypertrophic, and auricular-ventricular blocks or other conduction disorders due to lysosomal storage alteration. These can be produced by the structural alteration of the interventricular septum, rather than by biochemical alterations in pacemaker cells. This toxicity seems to be restricted to patients receiving high doses or long term treatment,<sup>6</sup> and it has been reported for treatment ranging from seven months<sup>3</sup> to 25 years.<sup>11</sup> At present, 12 cases of cardiac toxicity secondary to long term chloroquine treatment in systemic autoimmune diseases have been described (table 1). The doses of chloroquine in these patients ranged between 600 and 2281 g, and of hydroxychloroquine between 292 and 4380 g.

In a pathological examination<sup>8</sup> hypertrophy of myocardiocytes with heavily vacuolated cytoplasm and disorganisation of the myofibrillar architecture has been found. Electron microscopy shows dense residual bodies with folded membranous aggregates and curvilinear bodies. These changes were preferentially found in the cardiac septum,<sup>2</sup> and this might explain the involvement of the conduction system. This pathological pattern has not been seen in cardiac SLE without chloroquine treatment.<sup>7</sup>

In our patient the cause of biventricular cardiac failure was the hypertrophic cardiomyopathy. We excluded amyloidosis and haemosiderosis with a subcutaneous fat biopsy and ferritin determination. The SLE was not active, as the erythrocyte sedimentation rate, anti-DNA antibodies, and complement were normal. We considered that the cardiomyopathy was a chronic complication of chloroquine treatment, as the muscle biopsy showed. We did not perform an endomyocardial biopsy, because the muscular biopsy was positive. In addition, the patient also had other complications of long term treatment with chloroquine, such as retinopathy, myopathy, skin hyperpigmentation, and, probably, auditory impairment and hepatopathy.

We recommend that before starting long term treatment with chloroquine, cardiac evaluation with an ECG and an ophthalmological

examination are carried out. Chloroquine is not indicated if the patient presents some cardiac conduction disorder, in order to prevent cardiomyopathy or complete heart block. A six month ECG should be performed and, possibly, when the total dose of chloroquine is 1000 g or more, every year.

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Table 1 Cardiological complications in long term treatment with chloroquine and hydroxychloroquine in systemic autoimmune diseases. All the patients were female

Authors	Age	Disease	Cardiac complications	Other complications	Total dose
Verny <sup>3</sup>	56	SLE	CHB	Neuromyopathy	1168 g CQ
Verny <sup>3</sup>	55	MCTD	Right and left posterior blockade	Retinopathy	600 g CQ
Ratcliff <sup>4</sup>	59	SLE	CHF	NA	292 g HCQ
Ratcliff <sup>4</sup>	58	DL	CHF, CHB, RMC	NA	730 g HCQ, 1095 g CQ
Cubero <sup>5</sup>	59	DL	CHB, RMC	Myopathy, dead	2281 g CQ
Reuss-Borst <sup>6</sup>	73	RA	CHB	Neuromyopathy	912 g CQ
Reuss-Borst <sup>6</sup>	40	SLE	CHB	Retinopathy	NA
Baguet <sup>7</sup>	58	SLE	Right blockade, first degree block, HMC	Neuromyopathy	4380 g HCQ, 657 g CQ
Veinot <sup>8</sup>	60	RA, SS, Raynaud	CHB, CHF	Neuromyopathy, dead	912 g CQ
McAllister <sup>9</sup>	33	SLE	HMC	Myopathy	1003 g CQ
McAllister <sup>9</sup>	70	SLE	HMC	Dead	912 g CQ
Guedira <sup>10</sup>	43	RA	CHB	Hyperpigmentation	724 g CQ

SLE = systemic lupus erythematosus; MCTD = mixed connective tissue disease; DL = discoid lupus; RA = rheumatoid arthritis; SS = Sjögren's syndrome; CHB = complete heart block; CHF = congestive heart failure; RMC = restrictive myocardialopathy; HMC = hypertrophic myocardialopathy; CQ = chloroquine; HCQ = hydroxychloroquine; NA = not available.

## A pilot study of the salivary scintigraphy diagnostic performance in a Spanish population with Sjögren's syndrome diagnosed by the European criteria

The European classification criteria (ECC) include salivary scintigraphy (SSC) for diagnosing Sjögren's syndrome (SS).<sup>1</sup> The performance of this test has been established without considering the ECC for either confirming or excluding SS.<sup>1-6</sup> This pilot study aimed at evaluating the performance of the qualitative reading of SSC, performing a clinical measurement of SSC, and establishing the most discriminatory scintigraphic parameters for diagnosing SS in a Spanish population fulfilling the ECC.

This cross sectional study included consecutive patients referred for SSC: 15 healthy volunteers (eight women, seven men; mean (SD) age 50.6 (17.5)), 16 patients with SS based on the ECC (15 women, one man; age 58.1 (10.4)), and 15 xerostomic patients who did not fulfil the ECC, as controls (seven women, eight men; age 53.3 (19.0); AIDS (n=3), chronic parotitis (n=2), sarcoidosis (n=2), or taking drugs that cause dryness (n=8)).

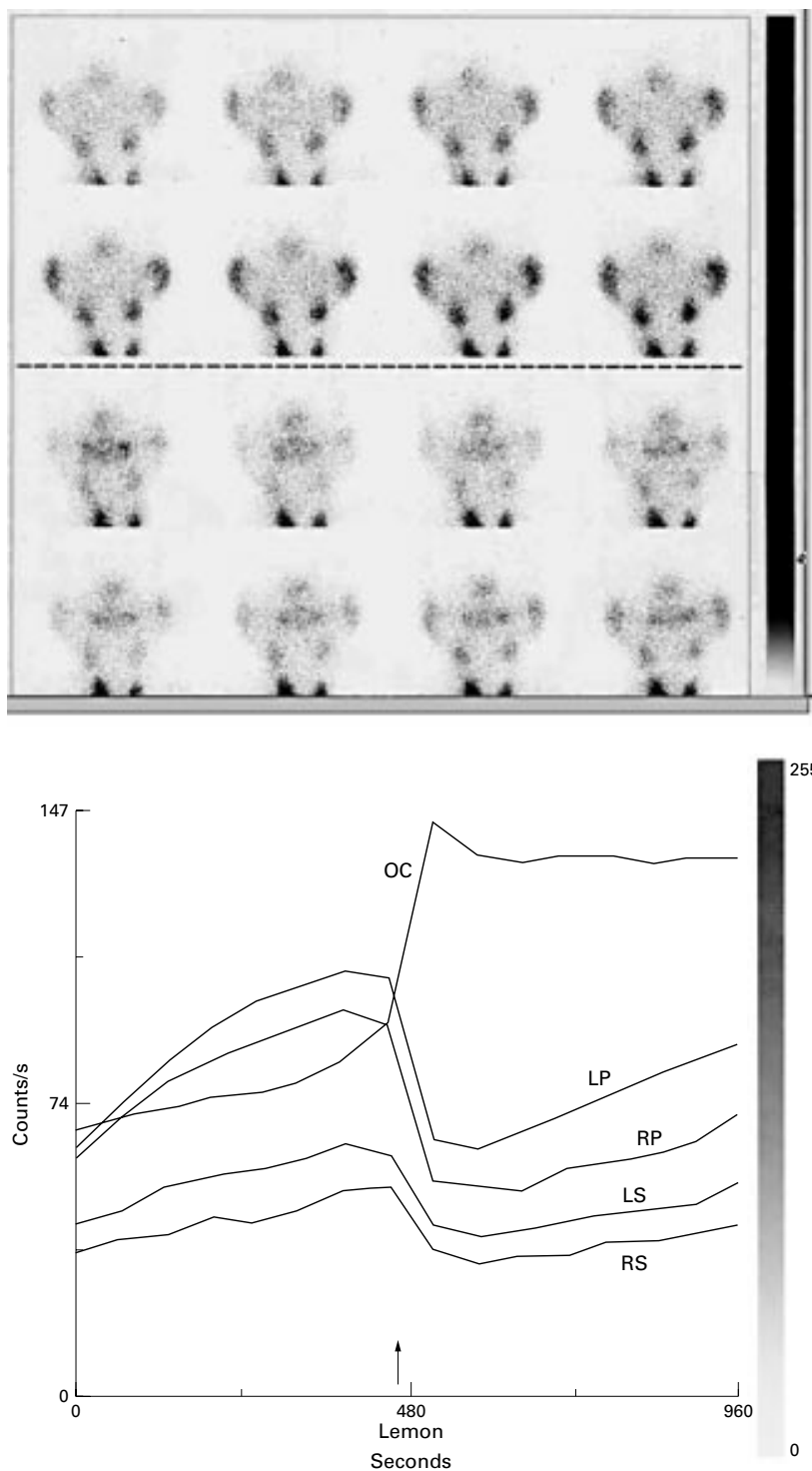
Patients underwent a sufficient number of tests included in the ECC set, if not all, to confirm or exclude SS. Scintigraphy was performed in patients and volunteers: image acquisition started two minutes after injection of technetium-99m pertechnetate, 60 second frames were continuously obtained for 16 minutes, and lemon juice given orally at 9.5 minutes. Data of the ECC set, except for scintigraphy, drug history, extraglandular manifestations of SS, associated connective tissue disease, and history of exclusion criteria, were collected by a questionnaire and from the medical records. SS was diagnosed according to the ECC.

Qualitative reading comprised visual evaluation of tracer accumulation and excretion by the parotid and submandibular glands in either the scan or the time-activity curves. Scintigraphy was positive for SS if both a sicca syndrome pattern<sup>7</sup> and a curve M, F, or S<sup>8</sup> were detected in at least two glands; it was negative if either positive in only one gland or normal (N curve<sup>8</sup> and normal pattern on the scan<sup>7</sup> in all glands; fig 1). Qualitative reading showed an excellent normalcy fraction (100%) and high sensitivity (87.5%) in detecting SS, but specificity was lower (66.7%). Sensitivity and specificity were as previously reported.<sup>1-6</sup> Some authors obtained better specificity by including healthy people as controls.<sup>9</sup> Predictive values (positive predictive value 73.7%, negative predictive value 83.3%) differed from those of other studies<sup>1-6</sup>; they are influenced by the prevalence of SS.

Clinical measurement was made on each gland curve measuring gland size (area), tracer accumulation, and stimulated excretion; these scintigraphic parameters were tabulated for all, parotid, submandibular, right and left glands. Clinical measurement in normal subjects generated a normal database that could be used to evaluate the inter- and intrapersonal variation of gland area and function in patients. ROC curves were plotted from parameters in patients, and optimal thresholds computed.

Optimal thresholds of area agreed well with the qualitative reading for diagnosing SS, and increased accuracy as a result of improved specificity with loss in sensitivity or normalcy fraction. They highly discriminated between patients with SS and controls, because areas significantly and exclusively decreased in

patients with SS compared with normal subjects and controls. The amount of acinar mass lost by the gland, is reflected by the smaller size of the gland on SSC. As patients with SS, normal subjects, and controls had similar ages, the gland size reduction may be considered as a characteristic scintigraphic



**Figure 1** Dynamic scan and time-activity curves of a normal scintigraphic study. Both parotid and submandibular glands show regular size and morphology. Tracer uptake by the salivary glands is uniform and similar to thyroidal uptake, and fast prompt excretion of the tracer into the oral cavity follows excretory stimulus. The time-activity curves show a phase of increased counts that corresponds to active radioisotope uptake: the parotid curves present a marked increase (RP = right parotid; LP = left parotid), higher than that of the submandibular glands (RS = right submandibular; LS = left submandibular). Stimulation with lemon juice is instantly followed by profuse excretion by both the parotid and submandibular glands, as note by a sharp fall in the curves of the glands and a spike in the oral time-activity curve (OC = oral cavity).

abnormality of SS. However, any conclusion must await a further extensive study.

Optimal thresholds of gland function were insufficiently accurate for diagnosis of SS, as they failed to discriminate between SS and controls, probably owing to different degrees of dysfunction in the patients with SS and the small sample size. We noted that tracer accumulation by the parotid gland decreased in sicca syndrome, but failed to show similar changes in submandibular uptake.<sup>9,10</sup> A decreased excretion fraction in all glands compared with normal is characteristic of sicca syndrome and not exclusive to SS as has been described.<sup>9,10</sup>

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## Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) as recurrence of aborted PMR

A comparison of clinical and laboratory findings in patients with RS3PE alone, PMR alone, and RS3PE associated with PMR has been recently published by Cantini *et al*.<sup>1</sup>

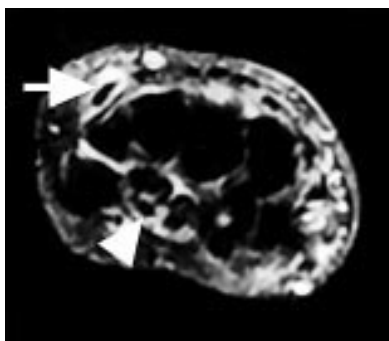


Figure 1 Dorsal hand swelling, mild synovitis, tenosynovitis of the extensor carpi ulnaris (arrow) and of the flexor tendons (arrowhead). Axial STIR image of the left wrist (TR/TE 1840/30; TI=85; NEX=1; matrix=180 × 180).

Their results suggest that the three conditions might represent a continuum, with PMR, a more severe condition, at one end and, RS3PE alone, at the other. PMR has a longer duration, is more commonly associated with systemic symptoms, requires higher doses of steroids for a longer time, and shows more relapses and recurrences. Although Cantini *et al* emphasised the similarities between PMR and RS3PE, they concluded that RS3PE alone is a separate entity. Other studies by the same group of authors have shown that RS3PE may be a feature of different diseases, such as spondyloarthropathies, psoriatic arthritis, rheumatoid arthritis (RA), acute sarcoidosis, and neoplasms.<sup>2</sup> Whether RS3PE is a distinct syndrome or a clinical feature of different inflammatory diseases is still unknown.

We have recently followed up a patient, whose disease course might help in interpreting the relation between PMR and RS3PE. This 76 year old man had a sudden onset of pain and stiffness in the shoulder and pelvic girdles in September 1997. Two days afterwards, he was seen by his general practitioner, who prescribed intramuscular betamethasone (4 mg daily for six days). A few days after completion of treatment, the patient was seen by one of us. At this time, physical examination was completely normal. In particular, no joint pain could be elicited and there were no signs of arthritis or tenosynovitis. His clinical history was unremarkable except for mild hypertension. Routine laboratory examinations performed before the onset of the disease, in January 1997, were normal with an erythrocyte sedimentation rate (ESR) of 1 mm/1st h. No further treatment was given and it was suggested that the patient called us if his symptoms recurred.

At the end of October, the patient again complained of joint pain and was admitted to our unit. At physical examination, there was pain at movement of the wrists and dorsal hand swelling with pitting oedema. There were no skin lesions compatible with psoriasis and no personal or family history of psoriasis. ESR was 38 mm/1st h and C reactive protein 12 mg/l (normal <5 mg/l). IgM rheumatoid factor, antinuclear antibodies, and a panel of antiviral antibodies were negative. Radiograms of hands and sacroiliac joints were normal. Magnetic resonance imaging (MRI) of the hands was performed by a dedicated extremity 0.2 T system (Artoscan, Esaote, Genova, Italy). Sequences included axial and coronal T<sub>1</sub> weighted gradient echo and short τ inversion recovery (STIR). Section thickness was 3.5 mm, interslice gap was 0.3 mm,

and the field of view was 11 cm. Tenosynovitis of the flexor and extensor tendons was seen in both hands, with mild synovitis in the left wrist (fig 1). A diagnosis of RS3PE was made and treatment with prednisone 5 mg/day and indometacin 50 mg at night was started. The signs and symptoms resolved completely after one week. Treatment was stopped after three months. Recently (June 2000), the patient is completely well with no recurrences of his disease.

This case report suggests that RS3PE may be the only clinical sign of recurrence in a patient with PMR. With the exception of the indexes of inflammation, which were not tested at disease onset, our patient fulfilled all the commonly accepted criteria for PMR.<sup>3</sup> Clinical features and MRI imaging of the recurrent disease were typical of RS3PE. It is tempting to speculate that early treatment of PMR might have aborted disease by downgrading the inflammatory response. If this is true, recurrence might have occurred at a more localised level of inflammation, represented by RS3PE. Two patients with PMR described by Healey had three subsequent episodes responsive to steroids, with typical signs of PMR, RS3PE, and seronegative RA.<sup>4</sup> In their series of RS3PE, Olivé *et al* studied two patients with PMR before RS3PE.<sup>5</sup> However, no precise description of the clinical features of these patients was given. These data confirm the view that PMR and RS3PE may be different manifestations of the same disease.

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## Antiphospholipid antibodies and RA: presence of $\beta_2$ GP1 independent aCL

Anticardiolipin antibodies (aCL) are found in many conditions, such as lupus erythematosus, but also in other connective tissue diseases like rheumatoid arthritis (RA). To determine the prevalence and significance of aCL in RA, we evaluated the frequency of anticardiolipin and anti- $\beta_2$  glycoprotein 1 ( $\beta_2$ GP1) antibodies in patients with RA.

We studied serum samples from 50 consecutive patients (36 women, 14 men) with RA



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)<sup>1</sup> 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  $\beta_2$ GP1 and differed from those using fetal calf serum, which are considered to add exogenous  $\beta_2$ GP1. aCL levels were expressed in IgM and IgG units (U), calculated by including serum samples calibrated with Harris's standards on every plate.<sup>2</sup> A search was made for IgG and IgM  $\beta_2$ GP1 antibodies by an ELISA using human  $\beta_2$ GP1 antigen coated on irradiated plates, according to Arvieux *et al.*<sup>3</sup> aCL and  $\beta_2$ 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  $\chi^2$  test or Fisher's test, as appropriate.

Nine patients (18%) had low titre IgG isotype aCL, but no  $\beta_2$ 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.<sup>4</sup>

$\beta_2$ GP1 antibodies were found in 8% of patients with RA, belonging to the IgM class in 75% of these cases. The sera containing IgM  $\beta_2$ GP1 antibodies also contained positive levels of RF. There was no correlation with any clinical manifestation.  $\beta_2$ GP1 antibodies were not found in healthy subjects.<sup>4</sup>

The frequency of aCL, all of them  $\beta_2$ GP1 independent in this study, was close to<sup>5</sup> or lower than in other studies (39–49%).<sup>6,7</sup> We found no association with clinical manifestations such as thrombotic events,<sup>8</sup> or extra-articular manifestations,<sup>9</sup> or with other autoantibodies (ANA).<sup>7,9</sup> The relation between IgM  $\beta_2$ 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".<sup>1</sup> The use of placebo studies for the development of new medicines in patients with rheumatoid arthritis (RA) remains controversial.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5</sup> 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.<sup>6</sup> Also, in three randomised controlled trials Sharp *et al* demonstrated retardation of radiographic progression by the use of leflunomide.<sup>7</sup> 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.

Dr García-Porrúa is a member of the Galician ethical committee for clinical investigation (northwestern Spain).

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