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), which is known to cause cardiac injury. In patients who develop a complete heart block and a restrictive cardiomyopathy, the use of 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.

Table 1

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age</th>
<th>Disease</th>
<th>Cardiac complications</th>
<th>Other complications</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verny1</td>
<td>56</td>
<td>SLE</td>
<td>CHB</td>
<td>Neutropathy</td>
<td>1168 g CQ</td>
</tr>
<tr>
<td>Verny1</td>
<td>55</td>
<td>MCTD</td>
<td>Right and left posterior block</td>
<td>Retinopathy</td>
<td>600 g CQ</td>
</tr>
<tr>
<td>Ratcliffe2</td>
<td>59</td>
<td>SLE</td>
<td>CHF</td>
<td>NA</td>
<td>292 g HCQ</td>
</tr>
<tr>
<td>Cüberso1</td>
<td>59</td>
<td>DL</td>
<td>CHF, CHB, RMc</td>
<td>Myopathy, dead</td>
<td>228 g CQ</td>
</tr>
<tr>
<td>Reuss-Borst3</td>
<td>73</td>
<td>RA</td>
<td>CHB</td>
<td>Myopathy, dead</td>
<td>913 g CQ</td>
</tr>
<tr>
<td>Baguet1</td>
<td>58</td>
<td>SLE</td>
<td>Right blockade, first degree block, HMC</td>
<td>Neutropathy</td>
<td>4380 g HCQ, 657 g CQ</td>
</tr>
<tr>
<td>Veinot1</td>
<td>60</td>
<td>RA, SS, Raynau</td>
<td>CHB, CHF</td>
<td>Myopathy, dead</td>
<td>912 g CQ</td>
</tr>
<tr>
<td>Guedria1</td>
<td>43</td>
<td>RA</td>
<td>CHB</td>
<td>Myopathy</td>
<td>1003 g CQ</td>
</tr>
</tbody>
</table>

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 myocardopathy; HMC = hypertrophic myocardopathy; QC = chloroquine; HCQ = hydroxychloroquine; NA = not available.

References:

Correspondence to: Dr R Cervera, Unitat de Malalties Autoimmune Sistemic, Hospital Clinic, University of Barcelona, Villarroel 170, 08036 Barcelona, Catalonia, Spain cervera@medicina.ub.es
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). The performance of this test has been established without considering the ECC for either confirming or excluding SS. 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 fulfill 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 and a curve M, F, or S were detected in at least two glands; it was negative if either positive in only one gland or normal (N curve and normal pattern on the scan 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. Some authors obtained better specificity by including healthy people as controls. Predictive values (positive predictive value 73.7%, negative predictive value 83.3%) differed from those of other studies; 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 stimuli. 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 diffuse 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).
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. 1


Antiphospholipid antibodies and RA: presence of β,γF1 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-β, γF1 protein 1 (β,γF1) antibodies in patients with RA.

We studied serum samples from 80 consecutive patients (36 women, 14 men) with RA...
The frequency of aCL, all of them β2GP1 independent in this study, was close to or lower than in other studies (39–49%).1 We found no association with clinical manifestations such as thrombotic events,3 or extra-articular manifestations,4 or with other autoantibodies (ANA).5,6 The relation between IgM β2GP1 antibodies and RA remains to be determined; it might be due to non-specific binding with RF.

C BONNET
P VERGNE
P BERTIN
R TREVES
Department of Rheumatology,
University of Limoges, France

M-O JAUBERTEAU
Department of Immunology,
University of Limoges, France

Correspondence to: Dr C Bonnet, Service de Rhumatologie, CHU Dupuytren, 2 Avenue Martin Luther-King, 87042 Limoges, France

1 Loizou S, Mc Crea JD, Rudge AC, Reynolds R, Boyle CC, Harris EN. Measurement of antiphospholipid antibodies by an enzyme-linked immunosorbent assay (ELISA) using microtisation 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; Diamond, 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 β2GP1 and differed from those using fetal calf serum, which are considered to add exogenous β2GP1. aCL levels were expressed in IgM and IgG units (U), calculated by including serum samples calibrated with Harris’s standards on every plate.7 A search was made for IgG and IgM β2GP1 antibodies by an ELISA using human β2GP1 antigen coated on irradiated plates, according to Arvieux et al.8 aCL and β2GP1 antibodies 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-DW1 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, steroids, treatment with disease modifying antirheumatic drugs, and treatment for other diseases, were reviewed. Statistical analysis was performed with the χ2 test or Fisher’s test, as appropriate.

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

<table>
<thead>
<tr>
<th>aCL+ patients (n=9)</th>
<th>aCL− patients (n=41)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) 63,2 ±/− 4</td>
<td>63,5 ±/− 12</td>
<td>NS</td>
</tr>
<tr>
<td>ANA* positive (titre &gt;160) 7 (77)</td>
<td>30 (73)</td>
<td>NS</td>
</tr>
<tr>
<td>Sjögren syndrome 4 (44)</td>
<td>12 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Extra-articular manifestations 4 (44)</td>
<td>6 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombosis history and/or abortion 1 (11)</td>
<td>3 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Steroid treatment 7 (77)</td>
<td>32 (78)</td>
<td>NS</td>
</tr>
<tr>
<td>DMARD* treatment 8 (88)</td>
<td>26 (63)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*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) using microtisation 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; Diamond, 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 β2GP1 and differed from those using fetal calf serum, which are considered to add exogenous β2GP1. aCL levels were expressed in IgM and IgG units (U), calculated by including serum samples calibrated with Harris’s standards on every plate.7 A search was made for IgG and IgM β2GP1 antibodies by an ELISA using human β2GP1 antigen coated on irradiated plates, according to Arvieux et al.8 aCL and β2GP1 antibodies 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-DW1 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, steroids, treatment with disease modifying antirheumatic drugs, and treatment for other diseases, were reviewed. Statistical analysis was performed with the χ2 test or Fisher’s test, as appropriate.

Nine patients (18%) had low titre IgG isotype aCL, but no β2GP1 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.9

β2GP1 antibodies were found in 8% of patients with RA, belonging to the IgM class in 75% of these cases. The sera containing IgM β2GP1 antibodies also contained positive levels of RF. There was no correlation with any clinical manifestation. β2GP1 antibodies were not found in healthy subjects.

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 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.4 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.5 Also, in three randomised controlled trials Sharp et al demonstrated retardation of radiographic progression by the use of leflunomide.6 Observations like these support the possible discontinualisation 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.7

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

C GARCIA-PORRÚA
M A GONZÁLEZ-GAY
Rheumatology Division,
Hospital Xeral-Calde, Lugo, Spain

Correspondence to: Dr M A González-Gay, Section of Rheumatology, Hospital Xeral-Calde Lugo, c/ Dr. Ochoa s/n, 27004 Lugo, Spain miguelaggay@hotmail.com


Cardiac toxicity secondary to long term treatment with chloroquine

À CERVERA, G ESPINOSA, R CERVERA, J FONT and M INGELMO

Ann Rheum Dis 2001 60: 301-302
doi: 10.1136/ard.60.3.301

Updated information and services can be found at:
http://ard.bmj.com/content/60/3/301

These include:

References
This article cites 11 articles, 2 of which you can access for free at:
http://ard.bmj.com/content/60/3/301#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/