Title: Antimalarial myopathy: an underdiagnosed complication?
Prospective longitudinal study of 119 patients.

Authors: . Enrique Casado, MD
. Jordi Gratacós, MD, PhD
. Carles Tolosa, MD, PhD
. José Miquel Martínez, MD
. Isabel Ojanguren, MD
. Aurelio Ariza, MD, PhD
. Jordi Real, Mr
. Angeles Sanjuan, MD
. Marta Larrosa, MD, PhD

Affiliations: 1Rheumatology Unit, 2Internal Medicine Department, 3Neurology Unit, 5Epidemiology Department and 6Orthopaedics Department, Parc Taulí University Hospital, and 4Department of Pathology, Germans Trias i Pujol University Hospital, Barcelona, Spain.

Corresponding author and address for reprint requests:
Dr Jordi Gratacós
Rheumatology Unit.
Parc Taulí University Hospital
Parc Taulí s/n. 08208 Sabadell, Barcelona, Spain
Telephone number: + 34 93 723 10 10 (Ext: 20232)
Fax number: + 34 93 716 06 46
E-mail address: jgratacos@cspt.es
ABSTRACT
Objectives: To evaluate the prevalence and incidence of antimalarial myopathy in patients with rheumatic diseases treated with antimalarial drugs.
Methods: Over a 3-year period, all patients with rheumatic diseases who were taking antimalarials were included. Serum muscle enzyme analysis at the time of inclusion and every 6 months was assessed in all patients. Muscle strength, electromyography (EMG) and muscle biopsy were performed in patients with a persistent muscle enzyme disturbance.
Results: 119 patients were included (111 chloroquine and 8 hydroxychloroquine). 22 patients (18.5%) had a persistent muscle enzyme disturbance: LDH 19/22 (86%); CK 7/22 (32%) and aldolase 3/22 (14%). Findings of antimalarial myopathy were detected in 3 of the 15 (20%) biopsied patients by light microscopy and in 15/15 patients (100%) by electron microscopy. Eleven patients had myopathy at the time of inclusion (prevalence 9.2%) and four patients developed muscle injury during follow-up (annual incidence of 1.2%). Muscle weakness was observed in 8 of 15 patients with biopsy-proven myopathy leading to a prevalence of clinical antimalarial myopathy of 6.7%. All of these patients also presented a myopathic pattern in the electromyographic study.
Conclusions: The prevalence of antimalarial myopathy is higher than previously recognized when the muscle enzyme determination is used as a screening method. When a persistent muscle enzyme disturbance is observed, a clinical and electromyographic study should be performed periodically to detect earlier the development of a clinical myopathy. In cases of clinical myopathy, an anatomopathological tissue study, including an ultrastructural one, is mandatory to confirm the diagnosis.

Keywords: antimalarial, chloroquine, hydroxychloroquine, myopathy
**INTRODUCTION**

Antimalarial drugs have proved to be beneficial in the treatment of a number of rheumatic diseases. It is thought that hydroxychloroquine sulphate is less toxic and has the same efficacy as chloroquine [1]. Thus, currently, hydroxychloroquine is more frequently used in most countries, although in some others, including Spain, chloroquine is still frequently prescribed.

Antimalarials have significant lysosomal affinity and induce the prominent development of autophagic vacuoles in several tissues [2-4]. Long-term administration of these drugs may result in accumulation of intracellular deposits, mainly in retina and muscle. Although myopathy is one of the most recognized toxic adverse effects, its prevalence in patients chronically treated with antimalarial drugs remains unclear. Several cases of antimalarial-induced myopathy, most of them isolated cases, have been reported [5-17]. Initial symptoms of muscular injury are characteristically mild. However, painless proximal weakness in both upper and lower extremities may become more severe in time. In many cases this clinical feature is masked by the musculoskeletal manifestations of the underlying disease, which could explain why the diagnosis of antimalarial myopathy is usually difficult and often delayed.

To determine the incidence and prevalence of antimalarial myopathy and its clinical consequences in patients with rheumatic diseases, we designed a longitudinal study using serum muscle enzyme analysis as a single sensitive screening method.

**METHODS**

A 3-year prospective longitudinal study was carried out in a Rheumatology Unit. All consecutive patients who had been taking antimalarial drugs at the time of inclusion for a period of at least 6 months were recruited. This minimum period of time was chosen because no cases of antimalarial myopathy within the first 6 months of treatment have been reported in the literature. One hundred and nineteen Caucasian patients were included in the study (84 female and 35 male; mean age: 57.5 ± 13.9 years). The underlying rheumatic disease was rheumatoid arthritis in 69 patients, palindromic rheumatism in 14, Sjögren syndrome in 11, systemic lupus erythematosus in 9, undifferentiated connective tissue disease in 7, psoriatic arthritis in 4 and other rheumatic condition in 5. One hundred and eleven patients were being treated with chloroquine and 8 with hydroxychloroquine. In all cases the daily prescribed amount of antimalarial drug did not exceed the recommended dose (3.5 mg/Kg/day for chloroquine and 6.5 mg/Kg/day for hydroxychloroquine). Mean duration of the treatment was 40.4 months (range: 6-192 months).

Serum muscle enzyme determinations served as the initial screening test in all patients, regardless of their clinical symptoms. The enzymes studied included lactodehydrogenase (LDH, normal value: 0-480 IU/l), creatine kinase (CK, normal value: 0-195 IU) and aldolase (normal value: 0-7.6 IU/l). Determinations were carried out at the time of inclusion and at 6-monthly intervals during the follow-up period in all patients, regardless of whether they had symptoms or not. The diagnostic algorithm used in the study is described in figure 1. Ethics approval was given for this study.

Myopathy was suspected in all patients who presented persistent muscle enzyme disturbance, defined as a rise in any one of the muscle enzymes...
measured in serum and confirmed in a second determination 2 or 3 weeks later. Other causes of myopathy or muscle enzyme increase, such as haemolysis, myocardial and renal infarction, low grade infections, chronic liver and pulmonary diseases and malignancy were excluded by clinical and analytical assessment. After an informed consent, all patients with persistent muscle enzyme disturbances underwent a muscle strength assessment, electromyographic study and muscle biopsy in order to establish a definitive diagnosis. A muscle biopsy would also be performed in any patient with clinical weakness, even with normal muscle enzymes.

- A complete neurological examination, including tendon reflexes, sensory and motor assessment, was carried out in all cases by the same physician (JMM) immediately after a persistent muscle enzyme disturbance was detected. Muscle strength was assessed on proximal and distal muscles of upper and lower limbs and on neck flexor muscles, and it was graded according to the standard 0-5 on the Medical Research Council scale. We considered muscle weakness as mild when muscle strength was 4+, moderate when it was between 3+ and 4, and severe when it was 3 or lesser in at least one muscle group.

- Electromyography and nerve conduction studies of proximal muscles of the upper and lower limbs were performed with surface electrodes and with standard methods, using the Viking IV electromyograph system (Nicolet, Biomedical, Madison, Wisconsin) in all patients with persistent muscle enzyme disturbances.

- An open biopsy was obtained from an electromyographically involved muscle group from each patient who had given the consent. If no significant electromyographic findings were present, a biopsy of either the deltoid or femoral quadriceps muscle was performed. Standard light and electron microscopic studies were carried out by the same pathologists (IO, AA) in each case. Briefly, tissue samples were frozen at −156°C in isopentane, cooled by liquid nitrogen. Transverse cryostat 10-20 µm-thick sections were stained with haematoxylin-eosin and Gomori’s modified trichrome for light microscopic study. Thin sections were subsequently stained with uranyl acetate and lead citrate for electron microscopic study. Antimalarial muscle toxicity was diagnosed only if the electron microscopic study showed evidence of curvilinear bodies, with or without myeloid bodies. Non-specific alterations such as vacuolar myopathy on light microscopy or free glycogen on electron microscopy were considered insufficient for diagnosis.

Definitions
- We defined antimalarial myopathy as the presence of the specific ultrastructural microscopic findings associated with persistent muscle enzyme disturbances, regardless of the clinical symptoms of the patients.
- We defined clinical antimalarial myopathy as the presence of antimalarial myopathy associated with an objective muscle weakness, through direct examination of proximal and distal muscles of upper and lower limbs and neck flexor muscles.

Statistical analysis. Statistical analysis was performed using an SPSS 11 database. Data is presented as mean ± SD or range, and percentages of total with Confidence Interval of 95% (CI 95%). T-Student and Levene tests were
used as appropriate for statistically significant differences between groups. Differences were considered statistically significant at $p < 0.05$.

**RESULTS**

Antimalarial myopathy, as defined above, was demonstrated in 12.6% of the patients included in the study. Eleven patients disclosed the myopathy at the inclusion point (prevalence of 9.2%) and four patients developed it during the follow-up period (annual incidence of 1.2%). The presence of symptoms of muscle weakness was observed in 6.7% of the patients included in the study, and in most cases (75%) these symptoms were mild to moderate. When the antimalarial treatment was withdrawn the clinical myopathy tended to disappear in all cases.

Twenty-two of the 119 patients included in the study (18.5%) had a persistent muscle enzyme disturbance. Raised LDH (mean value 646.3 IU/l; range 498-1282 IU/l) was the most frequent muscle enzyme disturbance (86%), and was the only increased muscle enzyme in 14 patients (64%). Seven patients (32%) showed raised CK serum levels (mean value 460 IU/l; range 201-1479 IU/l), however it is noteworthy that an isolated increase of CK was observed in only 3 patients (14%), and no patients showed an isolated increase of aldolase.

Muscle biopsy was performed in 15 of 22 patients with persistent muscle enzyme disturbances. Seven patients with persistent muscle enzyme disturbances dropped out of the study because of a detected neoplasm in one case, change of residence in three cases and consent denial in three more (figure 2). All the patients with persistent muscle enzyme disturbances biopsied presented specific findings of antimalarial muscle toxicity (lipid deposits of curvilinear and/or myeloid bodies), so they were diagnosed as antimalarial myopathy (figure 3). In contrast, vacuolar myopathy suggestive of antimalarial-induced toxic myopathy was seen only in 3 patients (20%) by light microscopy.

Eleven patients displayed the myopathy at the time of inclusion leading to a prevalence of 9.2% (95% CI: 4.0-14.4). A further 4 patients developed this complication during follow-up, which represents an annual incidence of 1.2% (95% CI: 0.03-2.4). Thus, the accumulated prevalence of antimalarial myopathy in the present study was 12.6% (95% CI: 6.6-18.5).

Eight of the 15 patients with antimalarial myopathy (53%) also showed muscle weakness on physical exploration, mild to moderate in 6 cases (75%) and severe in 2. Therefore, eight of the 119 patients included in the study proved to have clinical antimalarial myopathy, which represents a prevalence of 6.7% (95% CI: 4.8-8.6).

Electromyographic study showed a myopathic pattern in eight of 15 patients with antimalarial myopathy (53%), of who also had clinical myopathy. A muscle strength assessment and an electromyogram were also performed in 3 of the 7 patients who had dropped out of the study, all of which were normal.

Thirteen patients with antimalarial myopathy were being treated with chloroquine and two with hydroxychloroquine, although one of them had been receiving chloroquine at the onset of his rheumatic condition. Ten patients also received a maximum daily dose of 7.5 mg of prednisone or equivalent for their rheumatic disease. No other potential myotoxic drugs were prescribed and other causes of metabolic myopathy were ruled out. The main characteristics of patients with antimalarial myopathy are summarised in table 1.
It is noteworthy that any patient with normal muscle enzymes suffered from clinical weakness during the period of the study. The antimalarial treatment was withdrawn from the 7 patients with moderate to severe muscle weakness (muscle strength ≤4). Both signs and symptoms of clinical myopathy tended to disappear in all of them (table 2). One patient (case 7) had both neuropathic and myopathic findings on the electromyogram, although only the latter was recovered when the antimalarial drug was discontinued. Three patients died during follow-up. A patient suffered a myocardial infarction 2 years after complete recovery of the muscle enzyme disturbance; a second patient had a diverticulitis complicated with peritonitis and sepsis and unfortunately died 2 months after the diagnosis of the antimalarial myopathy; and another patient with previous diabetes and coronary artery disease died because of heart failure 3 years after the drug withdrawal and muscle enzyme normalisation (table 2).

DISCUSSION
The spectrum of muscle toxicity due to antimalarial drugs is extensive and in some cases controversial. The presence of the specific ultrastructural findings of antimalarial toxicity in muscle tissue may not always imply a muscle disease, but could be a muscular deposit of these drugs or their metabolites. In this sense Kumamoto [18] observed by electron microscope that experimental chloroquine-treated rats developed dense, membranous structures (curvilinear bodies) in soleus muscle fibres after the 8th day of intraperitoneal daily injections of chloroquine. In our study we only considered an antimalarial myopathy if the patient had both these specific histological findings and a persistent muscle enzyme disturbance, regardless of his clinical symptoms. With this consideration we found a prevalence of antimalarial myopathy of 9.2% and an annual incidence of 1.2%, because 4 new patients developed the myopathy during the follow-up period. This represents an accumulated prevalence of 12.6%. The higher number of patients with antimalarial myopathy at the beginning of the study has to be observed carefully. In fact we don’t know exactly since when these 11 patients (9.2%) had the myopathy, taking into account that most of them had been taking antimalarials for more than two years and that this complication can be present in a subclinical stage. Our results seem to be much higher than those suggested in previous retrospective, small and uncontrolled studies [5,10,11]. No report with prospective data on the incidence of antimalarial myopathy has been published to date. Avina-Zubieta et al [11] reported an antimalarial myopathy incidence of 1 in 100 patient-years of treatment, but their study was retrospective and certainly showed the frequency of clinical myopathy related to the time of treatment and not the true incidence of this complication. Furthermore, the differences between our study and other series [5,10,11] could be explained by the screening method used to reach the diagnosis of antimalarial myopathy. While earlier publications based their suspicion on the patient’s clinical manifestations, a persistent disturbance of any serum muscle enzyme was used as a starting point in the present study. We chose these biochemical tests because they were simple-to-perform and sensitive enough to detect muscle injury.

The serum muscle enzyme disturbance observed in most patients with myopathy in our study was mild, and LDH was, by far, the most sensitive
enzyme for detecting muscle illness just like it has previously been suggested in earlier publications [12]. However, it is well known that LDH is not specific for muscle disease, and can be found in other conditions, for example myocardial infarction, chronic liver and pulmonary diseases, haemolysis, renal and intestinal infarction, stroke, pulmonary emboli, pancreatitis, low-grade infections, neoplasias, and fractures, but in our patients these conditions were reasonably excluded (a patient with a hepatocarcinoma was excluded from the study). The fact that all patients with abnormal LDH from whom the antimalarial drug was withdrawn normalised their levels (table 2) would reinforce that the LDH increase had a muscular origin. We have no definite explanation for the poor sensitivity of CK as a screening tool, but low serum CK level is observed in some rheumatic diseases in relation to its inflammatory activity [19-21].

We disregarded using clinical manifestations as a starting point of our study as muscle weakness can be difficult to detect clinically. Furthermore, the underlying chronic rheumatism may mask muscle symptoms and can delay the diagnosis. However we also determined the prevalence of clinical myopathy, investigating how many of the 15 patients with antimalarial myopathy revealed signs or symptoms of muscle weakness. Some degree of muscle weakness was observed in 53% of the patients with antimalarial myopathy, that represent a prevalence of clinical myopathy of 6.7% in our study, a result quite high compared with previous series [5,10,11]. These differences can be explained again through the high sensitivity of the screening method we used, different from those applied in previous studies, specifically based on the patient’s symptoms. In addition, it is important to point out that only 2 (25%) of these patients developed a severe clinical disease, in accordance with their degree of muscle strength. We don’t have a muscle strength assessment of all the 119 patients treated with antimalarials, but in all patients with clinical antimalarial myopathy from whom we had data the muscle strength improved after the drug withdrawal (table 2), suggesting that the muscle weakness was caused by the antimalarials and not only by the underlying rheumatic disease.

It is known that the electromyogram is useful in the evaluation of any myopathy. However, our study revealed that its sensitivity was low for the diagnosis of antimalarial myopathy (53%), and therefore, it seems not advisable to use it as a unique diagnostic-screening tool in this context. However, all patients with clinical myopathy also had an abnormal electromyographic study, so this technique may be useful in the monitoring of patients with antimalarial myopathy to detect earlier the evolution of the disease from a subclinical to a clinical stage.

The confirmation of a suspicious diagnosis of antimalarial myopathy should be made through a histological study of the tissue samples. In our series, muscle biopsy was performed in all patients with persistent muscle enzyme disturbance, regardless of their clinical manifestations and/or electromyographic findings. In these cases an ultrastructural examination is absolutely mandatory to detect the characteristic tissue deposits that confirm the diagnosis of an antimalarial myopathy, since light microscopy has numerous false negatives (80% in our series). The 3 patients with vacuolar myopathy in the light microscopy had clinical involvement, with muscle strength impairment and electromyographic changes, which could mean that this technique may only detect the most advanced cases. Cytoplasmic complex lipid bodies (myeloid
and curvilinear bodies) constitute the characteristic features of antimalarial myopathy. In fact, these findings have not been detected in any other muscle illness except in ceroid lipofuccinosis, a rare lipid storage disease [22]. Whether or not these specific findings are seen in patients taking antimalarials without myopathy is not known, but all our biopsied patients did have muscle impairment on the basis of a muscle enzyme elevation.

During the follow-up, after the discontinuation of the antimalarial treatment in all patients with moderate to severe clinical myopathy, the muscle weakness, muscle enzyme disturbances and electromyographic changes tended to normalise as previously reported [9], enhancing the causality of antimalarials in the myopathy detected in our patients.

It has always been considered that hydroxychloroquine has lesser neuromuscular toxicity than chloroquine. Nevertheless, in the present study, a proven antimalarial myopathy was found in two of the eight patients taking this drug. Although the patient sample is insufficient to draw conclusions regarding this topic, this toxic myopathy may not be as rare as previously considered. More studies are required to establish the real prevalence of myopathy during treatment with hydroxychloroquine using some sensitive screening tools.

What clinical importance has the diagnosing of an antimalarial myopathy in asymptomatic patients? Should the antimalarial drug be withdrawn when a subclinical myopathy is detected in well-controlled patients? The high prevalence of this adverse effect may, in the future, make it advisable to recommend regular determinations of serum muscle enzymes in patients chronically treated with antimalarials. We opted for discontinuation of antimalarial treatment only in patients with clinical myopathy and to monitor the remaining patients (including a complete muscle strength test and an electromyographic study). A prospective controlled study to determine the likelihood of progression of a subclinical to a clinical myopathy is needed before definitive recommendations can be made.

CONCLUSIONS

In conclusion, this study suggests that the prevalence of antimalarial myopathy is much higher than previously recognised. Regular determinations of serum muscle enzymes, mainly LDH, seem to be a good screening method for the diagnosis suspicion of this myopathy. When a persistent muscle enzyme disturbance is detected, a clinical and electromyographic study should be carried out periodically to early establish the development of a clinical myopathy. In cases of clinical myopathy, an anatomopathologic tissue study, including an ultrastructural one, is mandatory to confirm the diagnosis, and the withdrawal of antimalarial drugs should be considered.
LIST OF ABBREVIATIONS:
LDH: lactodehydrogenase
CK: creatine kinase
CI: Confidence interval
EMG: electromyography
MRC: Medical Research Council
MB: Myeloid bodies
CB: Curvilinear bodies
CQ: Chloroquine
HCQ: Hydroxychloroquine
Myop: Myopathic
Myoneurop: Myoneuropathic
Neurop: Neuropathic
NA : Not available

COMPETING INTERESTS: None declared

The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in the Annals of the Rheumatic Diseases editions and any other BMJPLG products to exploit all subsidiary rights, as set out in our licence (http://ard.bmjournals.com/misc/ifora/licenceform.shtml).

AUTHORS’ CONTRIBUTIONS:
EC carried out the data collection and drafted the manuscript
JG coordinated the study and participated in its design. He provided some patients
CT provided some patients and contributed to the data collection
JMM carried out the muscle strength assessment and the electromyographic study
IO carried out the light and electronic microscopy of muscle samples
AA carried out the light microscopy of muscle samples
JR performed the statistical analysis
AS carried out the muscle biopsies
ML participated in the study design, provided some patients and cooperated in the coordination of the study

All authors read and approved the final manuscript

ACKNOWLEDGEMENTS
We wish to thank Mrs. Elena Fernández, nurse in Rheumatology, as without her collaboration this study would not have been possible, and to Miss Christine O’Hara and Mr. Neil Mc Leod for helping with the English version of the manuscript.
REFERENCES

Table 1. - Clinical, analytical and histological characteristics of patients with biopsy-proven antimalarial myopathy.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Underlying Disease*</th>
<th>Treatment</th>
<th>Duration of treatment</th>
<th>Daily dose</th>
<th>Laboratory† mean value</th>
<th>Muscle strength§</th>
<th>Electromyography</th>
<th>Light microscopy</th>
<th>Electron microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>68</td>
<td>RA</td>
<td>CQ</td>
<td>31 months</td>
<td>250 mg</td>
<td>LDH: 501.5</td>
<td>2/5</td>
<td>Myopathic</td>
<td>Vacuolar myopathy</td>
<td>CB, MB</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>73</td>
<td>RA</td>
<td>CQ</td>
<td>23 months</td>
<td>250 mg</td>
<td>LDH: 1152 CK: 1497</td>
<td>4/5</td>
<td>Myopathic</td>
<td>Vacuolar myopathy</td>
<td>MB</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>77</td>
<td>RA</td>
<td>CQ</td>
<td>26 months</td>
<td>250 mg</td>
<td>LDH: 587</td>
<td>4/-5</td>
<td>Myopathic</td>
<td>Vacuolar myopathy</td>
<td>CB, MB</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>77</td>
<td>Psoriatic Arthritis</td>
<td>HCQ</td>
<td>74 months</td>
<td>400 mg</td>
<td>LDH: 1282 Aldolase: 23</td>
<td>4/5</td>
<td>Myopathic</td>
<td>Normal</td>
<td>CB, MB</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>78</td>
<td>RA</td>
<td>CQ</td>
<td>28 months</td>
<td>250 mg</td>
<td>LDH: 661</td>
<td>1/5</td>
<td>Myopathic</td>
<td>Normal</td>
<td>CB, MB</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>28</td>
<td>SLE</td>
<td>HCQ</td>
<td>12 months</td>
<td>400 mg</td>
<td>CK: 201.7</td>
<td>5/5</td>
<td>Normal</td>
<td>Fibres atrophy</td>
<td>CB</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>74</td>
<td>RA</td>
<td>CQ</td>
<td>62 months</td>
<td>250 mg</td>
<td>LDH: 546</td>
<td>4/5</td>
<td>Myopathic and neuropathic</td>
<td>Normal</td>
<td>CB</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>57</td>
<td>RA</td>
<td>CQ</td>
<td>76 months</td>
<td>250 mg</td>
<td>CK: 276.3</td>
<td>5/5</td>
<td>Normal</td>
<td>Fibre atrophy</td>
<td>CB, MB</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>65</td>
<td>RA</td>
<td>CQ</td>
<td>26 months</td>
<td>250 mg</td>
<td>LDH: 506</td>
<td>5/5</td>
<td>Normal</td>
<td>Normal</td>
<td>MB</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>61</td>
<td>RA</td>
<td>CQ</td>
<td>104 months</td>
<td>250 mg</td>
<td>LDH: 610</td>
<td>5/5</td>
<td>Normal</td>
<td>Normal</td>
<td>CB, MB</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>59</td>
<td>RA</td>
<td>CQ</td>
<td>70 months</td>
<td>250 mg</td>
<td>LDH: 572 CK: 255.5</td>
<td>4/5</td>
<td>Myopathic</td>
<td>Fibre atrophy</td>
<td>CB, MB</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>39</td>
<td>Pal. R.</td>
<td>CQ</td>
<td>11 months</td>
<td>250 mg</td>
<td>CK: 213</td>
<td>5/5</td>
<td>Normal</td>
<td>Normal</td>
<td>CB, MB</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>53</td>
<td>S.S.</td>
<td>CQ</td>
<td>6 months</td>
<td>250 mg</td>
<td>LDH: 498</td>
<td>5/5</td>
<td>Normal</td>
<td>Normal</td>
<td>CB, MB</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>64</td>
<td>S.S.</td>
<td>CQ</td>
<td>68 months</td>
<td>250 mg</td>
<td>LDH: 532.3 CK: 319.7</td>
<td>5/5</td>
<td>Normal</td>
<td>Fibre atrophy</td>
<td>CB</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>62</td>
<td>RA</td>
<td>CQ</td>
<td>30 months</td>
<td>250 mg</td>
<td>LDH: 554.7</td>
<td>4+/5</td>
<td>Myopathic</td>
<td>Fibre atrophy</td>
<td>CB</td>
</tr>
</tbody>
</table>

* M: Male; F: Female.  
†: CQ: Chloroquine; HCQ: hydroxychloroquine.  
‡: Normal laboratory values: Lactodehydrogenase (LDH): 0-480 IU/l; creatine kinase (CK): 0-195 IU/l; Aldolase: 0-7.6 IU/l.  
§: Muscle strength: according the standard 0-5 MRC scale.  
¶: MB: myeloid bodies; CB: curvilinear bodies.
Table 2.- Evolution of serum muscle enzyme levels, muscle weakness and electromyographic findings in patients with moderate and severe clinical antimalarial myopathy after drug withdrawal.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; Sex*</th>
<th>Treatment#</th>
<th>Laboratory‡ (before/after+)</th>
<th>Muscle weakness§ (before/after+)</th>
<th>Electromyography† (before/after+)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68M</td>
<td>CQ</td>
<td>LDH 501/389</td>
<td>+++/+</td>
<td>Myop/Normal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>73F</td>
<td>CQ</td>
<td>LDH 1152/436</td>
<td>++/-</td>
<td>Myop/Normal</td>
<td>Death (Myocardial infarction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CK 1497/38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>77F</td>
<td>CQ</td>
<td>LDH 587/459</td>
<td>++/-</td>
<td>Myop/Normal</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>77F</td>
<td>HCQ</td>
<td>LDH 1282/NA</td>
<td>++/NA</td>
<td>Myop/NA</td>
<td>Death (sepsis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aldolase 23/NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>78F</td>
<td>CQ</td>
<td>LDH 661/466</td>
<td>+++/-</td>
<td>Myop/Normal</td>
<td>Death (Heart failure)</td>
</tr>
<tr>
<td>7</td>
<td>74F</td>
<td>CQ</td>
<td>LDH 546/403</td>
<td>++/-</td>
<td>Myoneurop/Neurop</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>59F</td>
<td>CQ</td>
<td>LDH 572/449</td>
<td>++/-</td>
<td>Myop/Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CK 255/91</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: M: Male; F: Female.
#: CQ: Chloroquine; HCQ: Hydroxychloroquine.
‡: Normal laboratory values: LDH 0-480 IU/l; CK 0-195 IU/l; Aldolase 0-7.6 IU/l.
*: before: before antimalarial withdrawal; after: after antimalarial withdrawal.
§: Muscle weakness: + mild; ++ moderate; +++ severe, as defined on patients and methods.
†: Myop: Myopathic pattern; Myoneurop: Myoneuropathic pattern; Neurop: neuropathic pattern. NA: Not available.
Patients on chronic antimalarial treatment (more than 6 months) for a rheumatic disease

Serum muscle enzymes (LDH, CK, Aldolase)

Raised in $\geq 2$ determinations

Normal

Follow-up (every 6 months)

Muscle strength
Electromyography
Muscle biopsy (Light and electron microscopy)
Figure 2: Flow of patients in our study

119 patients under antimalarial treatment for rheumatic diseases

- Muscle enzyme rise: 22/119 (18.5%)
- Normal muscle enzymes: 96/119

Follow-up study: 15 patients

- Lost from the study: 7 patients

Electromyography + Muscle biopsy: 15 patients

- EMG
- Muscle biopsy

- Myopathic pattern: 8/15 patients (53%)
- Normal: 7/15 patients (47%)

Light microscopy

- Normal or nonspecific: 12/15 patients
- Vacuolar myopathy: 3/15 patients
- Antimalarial myopathy: 15/15 patients

Electron microscopy
Figure 3. - Sarcoplasm of a muscle fibre showing the characteristic findings of antimalarial myopathy: Myeloid bodies (arrow) and curvilinear bodies (asterisk). (ME, x13000)