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ORIGINAL ARTICLE

# Quinacrine in the Treatment of Cutaneous Lupus Erythematosus: Practical Aspects and a Case Series

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**Abstract**
Hydroxychloroquine and chloroquine are antimalarials used as first-line treatment of cutaneous lupus. Quinacrine is not often employed by Spanish physicians due to a lack of information about its use and the fact that it is not marketed in Spain. It is effective in monotherapy or in combination therapy with other antimalarials. One of the advantages of quinacrine over chloroquine and hydroxychloroquine is that it does not appear to cause retinal toxicity.
Quinacrine is used as second-line therapy in patients with pre-existing eye problems that contraindicate treatment with chloroquine or hydroxychloroquine (after evaluation of which drug has the better risk-benefit relationship), and in combination therapy with other antimalarials in patients with resistance or only a partial response to chloroquine or hydroxychloroquine.
We report 8 cases of patients with cutaneous lupus who received treatment with quinacrine in monotherapy or in combination with other antimalarials. Lesions resolved in 5 patients and improved in 3. Therapy had to be withdrawn in 1 patient due to an exacerbation of his psoriasis.


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**PALABRAS CLAVE**
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Efecto secundario

## Aspectos Prácticos de la Quinacrina Como Tratamiento del Lupus Eritematoso Cutáneo: Serie de Casos

### Resumen

Los antimaláricos de primera elección en el tratamiento del lupus cutáneo son la hidroxicloroquina (hydroxychloroquine) y la cloroquina (chloroquine). La quinacrina (Qn) se emplea poco, fundamentalmente por la ausencia de información sobre su utilización y por no estar comercializada en España. Es eficaz en combinación con otros antimaláricos y en monoterapia. La quinacrine parece carecer de toxicidad retiniana y ésta es una de sus ventajas sobre la chloroquine y la hydroxychloroquine.

Se utiliza cuando existen alteraciones oculares previas al tratamiento que contraindican el uso de otros antimaláricos (al valorar la opción con mejor relación riesgo-beneficio), y en tratamiento combinado con otros antimaláricos en pacientes resistentes o parcialmente respondedores a chloroquine o hydroxychloroquine.

Presentamos una serie de 8 casos de pacientes con lupus cutáneo que han recibido tratamiento con quinacrine en monoterapia o combinada con otros antimaláricos, se obtuvo resolución de las lesiones en 5 pacientes y mejoría de éstas en 3 pacientes. En uno de los pacientes fue necesario suspender el tratamiento por la aparición de un brote de psoriasis.



## Introduction

Therapeutic options for the treatment of cutaneous lupus erythematosus include photoprotection, topical and intralesional corticosteroids, and antimalarial agents. Of the antimalarials, first-line treatments are chloroquine and hydroxychloroquine. A third antimalarial option is quinacrine, but this is not often used by Spanish physicians because it is not marketed in Spain and there is a lack of information about its use.

We report a series of 8 patients with different forms of cutaneous lupus who were treated with quinacrine alone or in combination with other antimalarials. We also discuss practical aspects regarding the use of quinacrine.

## Patients and Methods

We describe a series of 8 patients, aged between 22 and 67 years (mean, 48 years), who were diagnosed with the following forms of cutaneous lupus: chronic cutaneous lupus, subacute cutaneous lupus, lupus panniculitis, and acute cutaneous lupus. Four of the patients fulfilled criteria describing systemic lupus erythematosus.

Four patients had failed to respond to successive treatments with hydroxychloroquine and chloroquine, and 1 patient had failed to respond to chloroquine; the indication for quinacrine treatment in the 3 remaining patients was a visual disorder, with or without prior antimalarial treatment (Table 1). Treatments were as follows: 3 patients received chloroquine (250 mg/d) and quinacrine (100 mg/d), 2 patients received hydroxychloroquine (200 mg/d) and quinacrine (100 mg/d), and 3 patients received quinacrine as monotherapy (100 mg/d). Table 1 shows the duration of treatment for each patient (mean, 8.5 months).

Since quinacrine is not authorized for use in Spain, it was necessary to make a compassionate-use request through our hospital pharmacy service. To this end, patients were required to provide written informed consent in the presence of a witness. Laboratory tests, consisting of a complete blood count, biochemistry, and coagulation tests, were performed prior to commencing treatment and several times during the treatment period, with no changes observed in the results. Ophthalmic evaluations were also performed before and during the treatment, either because patients were receiving other antimalarial agents in combination or because they had previously had a retinal disorder.

## Results

Response to treatment was evaluated according to the following clinical criteria: complete resolution of the lesions or persistent inactivity of residual lesions; a good response (significant improvement in over 50% of lesions); and no response. Lesions resolved in 5 of the 8 patients, and response was good in the remaining 3 patients. All the patients showed good tolerance to the treatment.

A brownish-yellow discoloration of the skin was observed in 4 of the patients, but this was well tolerated given that it resembled a darker skin complexion. This discoloration disappeared in all the patients within a few months after treatment ended. Treatment was suspended in 1 patient due to an outbreak of psoriasis, which was treated with systemic methotrexate.

## Discussion

Quinacrine, a synthetic quinine derivative, was used as a prophylactic treatment for malaria during World War 2, when it was observed that soldiers with lupus and rheumatoid arthritis receiving quinacrine experienced an

**Table 1** Diagnosis, indication, treatment, and treatment outcomes for 8 patients with cutaneous lupus

| Diagnosis | Sex | Age, y | Indication | Treatment | Adverse effects | Response |
|---|---|---|---|---|---|---|
| ACL<br>SLE (fig. 1a-b) | F | 22 | Poor response to CQ (250 mg/d for 12 mo) | CQ (250 mg/d)<br>QN (100 mg/d for 4 mo) | Skin discoloration | Resolution |
| ACL<br>SLE | F | 52 | Poor response to CQ (250 mg/d for 12 y) and HCQ (400 mg/d for 3 y) | HCQ (200 mg/d<br>QN (100 mg/d for 3 mo)* | No | Good |
| LP<br>LET | M | 40 | Dyschromatopsia with CQ (250 mg/d for 18 mo) | QN (100 mg/d for 12 mo) | No | Resolution, but with flare following suspension, good response thereafter |
| CCL (fig. 2a-b) | M | 31 | Maculopathy due to congenital rubeola | QN (100 mg/d for 5 mo) | Skin discoloration | Resolution |
| CCL<br>ACL<br>SLE<br>(fig. 3a-b) | F | 30 | Visual field defect due to HCQ (200 mg/d for many years for rheumatology) | QN (100 mg/d for 12 mo) | Skin discoloration<br>psoriasis | Good. Suspended due to psoriasis outbreak |
| CCL | F | 67 | Poor response to HCQ (200 mg/d for 1 y) and CQ (500 mg/d) | HCQ (200 mg/d)<br>QN (100 mg/d for 11 mo) | Skin discoloration | Inactivity |
| CCL<br>SACL | F | 34 | Poor response to HCQ (200 mg/d for 6 mo) and CQ (500 mg/d for 6 mo) | CQ (250 mg/d) and QN (100 mg/d for 3 mo) | No | Resolution |
| CCL | F | 35 | Poor response to HCQ (200 mg/d for 9 mo) and CQ (250 mg/d for 2 mo) | CQ (250 mg/d) and QN (100 mg/d for 18 mo) | No | Good |

Abbreviations: ACL, acute cutaneous lupus; CCL, chronic cutaneous lupus; CQ, chloroquine; HCQ, hydroxychloroquine; LET, lupus erythematosus tumidus; LP, lupus panniculitis; QN, quinacrine; SACL, subacute cutaneous lupus; SLE, systemic lupus erythematosus.

*HCQ suspended due to scotomata, QN treatment maintained (100 mg/48 h).

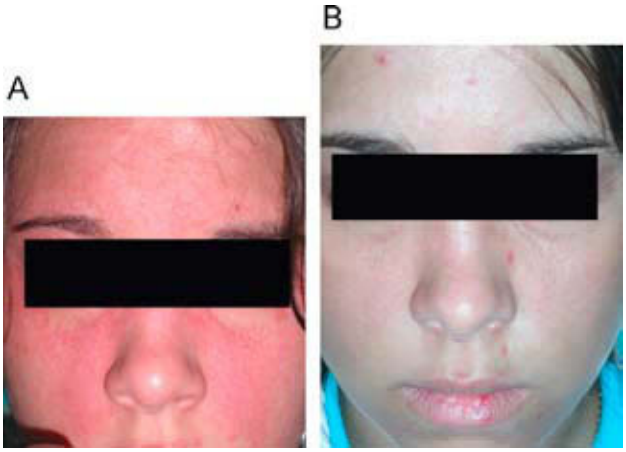


**Figure 1** A) Slightly scaly erythematous plaques on the cheekbones and forehead, prior to treatment. B) Lesions resolved by treatment.

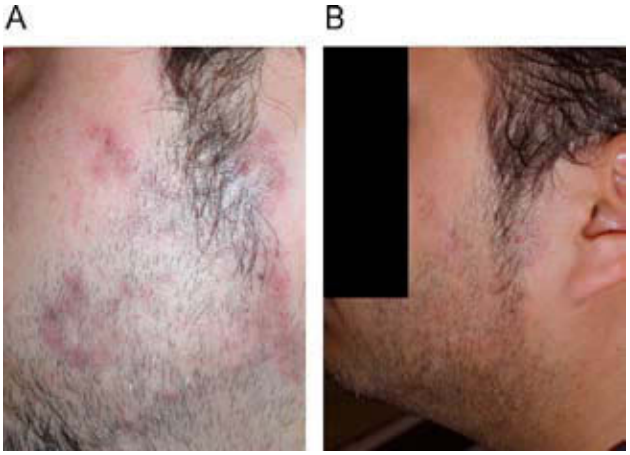


**Figure 2** A) Violaceous erythematous plaques with slight central atrophy in the left preauricular region prior to treatment. B) Lesions resolved by treatment.

improvement in these conditions. Following on from this observation, in 1951 Page[1] described a series of patients with discoid lupus who responded well to quinacrine. Use of quinacrine as an antimalarial agent declined, however, as a result of the development of other more effective quinine derivatives, such as chloroquine.

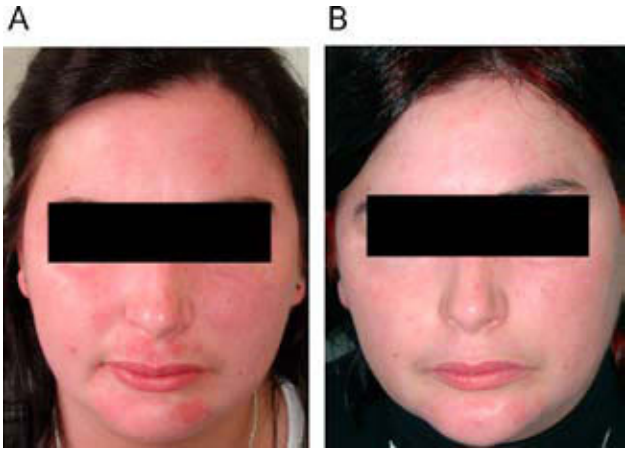


**Figure 3** A) Scaly erythematous plaques on the face prior to treatment. B) Lesions that responded well to treatment.

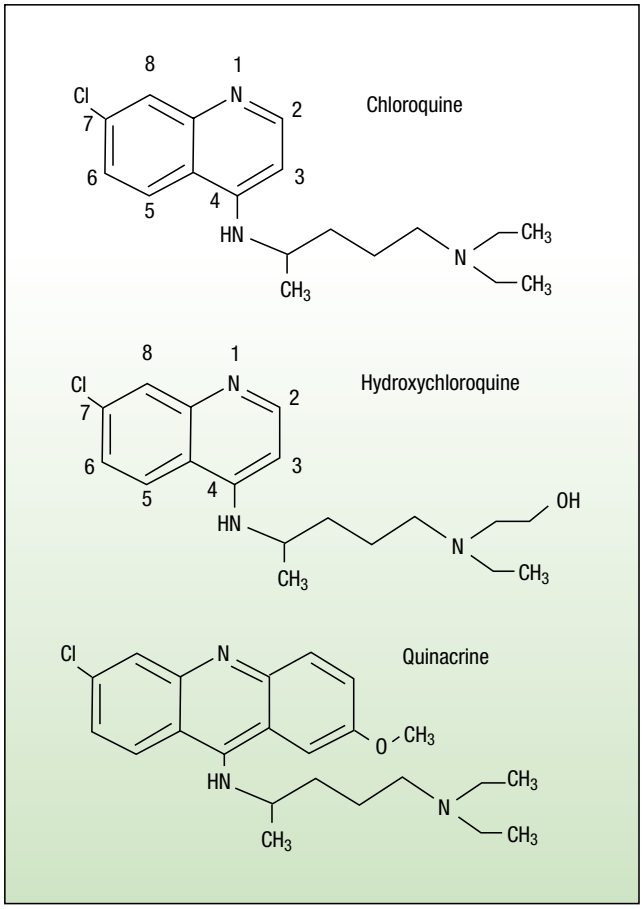


**Figure 4** Chemical structure of chloroquine, hydroxychloroquine, and quinacrine antimalarial agents.

A quinacrine preparation in combination with another antimalarial agent (chloroquine or hydroxychloroquine) was subsequently marketed for the treatment of discoid lupus.[2] At the end of the 1970s, however, this preparation, along with many other combination therapies, was withdrawn from the market by the US Food and Drug Administration. As it does not have local marketing approval, quinacrine can only be obtained in Spain by placing a request with a hospital pharmacy service.

It is recommended not to use chloroquine and hydroxychloroquine together as they have similar therapeutic and ocular toxicity profiles.

The presence of an extra benzene ring makes the chemical structure of quinacrine different from that of chloroquine and hydroxychloroquine (Figure 4). This may explain why there is no quinacrine crossreactivity with chloroquine or hydroxychloroquine, and also why quinacrine does not potentiate adverse effects when combined with either chloroquine or hydroxychloroquine. The pharmacokinetics of these drugs are similar.[3]

A notable advantage of quinacrine is the absence of retinal toxicity; only 2 cases of retinopathy have been reported, and in neither was it possible to establish a clear cause-effect relationship.[4,5] One of these patients received quinacrine during 18 months as a prophylaxis for malaria; some 40 years later and with no exposure to other possible explanatory factors, the patient developed bull's eye maculopathy.[4] The other patient was treated with 100 mg/d of quinacrine for 12 years, but it was not reported whether this patient had received other antimalarial agents.[5] Regular ophthalmic assessments were carried out in all our patients—both those who received quinacrine as monotherapy because hydroxychloroquine and chloroquine were contraindicated, and those who received it in combination with hydroxychloroquine and chloroquine. However, no worsening of the baseline condition or newly developed visual disorders were detected. Quinacrine monotherapy, therefore, is a possible alternative treatment for cases in which either hydroxychloroquine or chloroquine is contraindicated. Note, nonetheless, that a limitation of our study is the small number of patients included.

Aplastic anemia, a serious and potentially fatal disorder, is a possible side effect of quinacrine. A higher incidence of aplastic anemia was observed in soldiers treated with quinacrine during World War 2, with the rate rising from 0.66 per 100 000 patients to 2.84 per 100 000 patients. A third of these cases were attributed to quinacrine overdose or concomitant use of other causal agents, such as the sulfonamides. Of the remaining cases, around 70% of patients presented with a lichenoid reaction several months prior to the onset of the aplastic anemia. Consequently, the risk of aplastic anemia developing in quinacrine-treated patients who experience no lichenoid eruption is estimated as 1 per 500 000 patients.[6] Performing a complete blood count every 3 months is crucial, since aplastic anemia can be averted by discontinuing quinacrine at the onset of the hypocellular phase of this condition. The incidence of aplastic anemia also seems to be correlated with dosage and treatment duration. In the cases described, the patients with lupus and rheumatoid arthritis had received doses of over 100 mg/d, up to 50% had had a previous lichenoid reaction, and blood tests had been conducted very infrequently.[7] None of the test results for our patients necessitated treatment interruption or dose reduction. It should be emphasized that blood testing must be periodic to ensure detection of the hypocellular phase of aplastic anemia.

Other adverse effects of quinacrine are headache and gastrointestinal symptoms, which occur in up to a third

**Table 1** Practical Aspects of Quinacrine Treatment

| | |
|---|---|
| Indications | • Patients with cutaneous lupus who:<br>○ Are resistant to other antimalarials<br>○ Have ocular disorders that contraindicate other antimalarials |
| Adverse effects | • Headache<br>• Gastrointestinal symptoms<br>• Yellowish discoloration of skin and mucosa<br>• Aplastic anemia<br>• Psychosis, convulsions |
| Contraindications | • Hypersensitivity to quinacrine<br>• Exercise caution with:<br>○ Patients with G-6PD deficit<br>○ Patients with blood dyscrasias<br>○ Patients with bipolar disorders<br>○ Patients with liver disorders<br>○ Patients with psoriasis<br>○ Patients with porphyria<br>○ Women who are pregnant or breastfeeding |
| Recommendations | • Maximum dose 100 mg/d<br>• Suspend treatment if no response within 6-8 wk<br>• Perform blood count and biochemistry analyses at baseline, monthly for 3 mo, and thereafter every 3 mo<br>• Perform baseline and yearly ophthalmic evaluation<br>• Suspend treatment due to aplastic anemia risk if a lichenoid eruption occurs |

Abbreviation: G-GPD, glucose-6-phosphate dehydrogenase.

of patients, but which tend to resolve on reducing the dose. Another adverse effect is that, in the first weeks of treatment, the skin may acquire a yellowish tone and develop sclerotic lesions; these conditions resolve, however, once treatment is suspended. Finally, as happens with other antimalarial agents—and as happened with 1 of our patients—psoriasis may worsen.

In the literature, we identified 3 case series involving patients with cutaneous[8,9] or systemic lupus[10] that was refractory to treatment (including with hydroxychloroquine, chloroquine, retinoids, thalidomide, and dapsone) and in whom a good response was obtained with quinacrine in combination with chloroquine or hydroxychloroquine.

When prescribing antimalarial treatment in her own practice, Victoria Werth[11] first prescribes hydroxychloroquine (maximum dose, 6.5 mg/kg/d) and, if necessary, combines it with quinacrine (100 mg/d). If an adequate therapeutic response is not observed after 6-8 weeks of combined treatment, she maintains quinacrine but switches from hydroxychloroquine to chloroquine (maximum dose, 3.5 mg/kg/d).

Chung et al[12] described the case of a patient with lupus panniculitis resistant to treatment with oral corticosteroids as monotherapy or combined with hydroxychloroquine, reporting resolution of the lesions following a switch to hydroxychloroquine combined with quinacrine.

We obtained similar results to those reported in the literature, with resolution or improvement of refractory cutaneous lupus following treatment with quinacrine in combination with either chloroquine or hydroxychloroquine.

We underline the importance of being aware of quinacrine as a treatment option for cutaneous lupus (Table 2), whether as monotherapy or in combination with another antimalarial agent. We are of the opinion that quinacrine is particularly indicated in the following circumstances:

- As a second-line treatment with a good risk-benefit profile for patients with ocular alterations in which other antimalarial agents are contraindicated. Although ocular disorders have not been reported in patients treated with quinacrine, this may be related to dose and treatment duration (doses above 100 mg/d are not recommended).
- As a combination therapy for patients with lupus resistant to other antimalarial agents.

## Conflicts of Interest

The authors declare no conflicts of interest.

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