

## Effectiveness of Quinacrine (Mepacrine) in Photosensitive Autoimmune Diseases, Lupus Erythematosus, and Dermatomyositis: Report on 38 Cases and Literature Review

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### ABSTRACT

**Objectives:** This study aims to report our experience with photosensitive autoimmune diseases including lupus erythematosus and dermatomyositis (DM) treated with quinacrine (Qn) as either monotherapy or combination with other antimalarials, steroids, and immunosuppressive therapy in an add-on regimen in light of a review of the relevant literature.

**Patients and methods:** The study included 38 patients (6 males, 32 females; mean age 45±8 years; range, 23 to 72 years) with systemic lupus erythematosus (SLE), cutaneous lupus or DM who had been treated with Qn. The following data were obtained from the records of each patient: sex, age, diagnosis, duration of the disease, duration of treatment, smoking behavior, antimalarial treatment, concomitant treatment, and clinical indications, as well as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity before initiation, at the last visit, or when Qn treatment was completed. We carried out a MEDLINE search for previously reported cases that, together with our patients, served as the basis of this report.

**Results:** Of the 38 patients, 34 were suffering from SLE or cutaneous lupus and four from DM. Qn was dosed at 50 or 100 mg in most of the patients. Twenty-seven patients received Qn as an add-on regimen therapy. Clinical response was analyzed in patients with SLE or cutaneous lupus. Of the patients, 25 responded (68.4%), 13 (52%) had improved CLASI activity and 12 (48%) had improved SLEDAI score. Fifty percent of the patients with DM responded. A total of 188 cases were identified from the literature. The most frequent diagnosis was cutaneous lupus (68.6%), followed by SLE (32.6%). Only 7.4% of the patients had DM. The majority of the patients received concomitant immunosuppressive medications. Treatment response was 73% in patients with SLE and/or cutaneous lupus and 35.7% in patients with DM. Side effects were scarce and the most frequent was yellow skin discoloration.

**Conclusion:** Quinacrine may be an alternative for patients with poor response or those who are intolerant to other antimalarials. Thus, Qn may aid in controlling the activity of photosensitive autoimmune diseases.

**Keywords:** Antimalarials; cutaneous lupus erythematosus; dermatomyositis; mepacrine; quinacrine; systemic lupus erythematosus.

For years, antimalarials have been used to treat several autoimmune diseases.<sup>1</sup> The efficacy of antimalarials is related to a strong modulation of the immune response,<sup>2</sup> as well as their photoprotective properties.<sup>3</sup> Hydroxychloroquine (HCQ) and chloroquine (CQ) are often the first-choice therapy. Quinacrine (Qn) is used as second-line therapy,

particularly in patients with pre-existing eye conditions for which treatment with HCQ or CQ is contraindicated, and in combination with other antimalarials in patients with treatment-resistance or only a partial response to CQ or HCQ.<sup>4</sup> A 1,959 study showed the strength of Qn used with HCQ,<sup>5</sup> and combination therapy has been used since.<sup>6</sup>

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In patients with lupus erythematosus (LE), combining low, medium, or high doses of glucocorticoids with another antimalarial drug (HCQ or CQ) or just with Qn seems to be a good choice for helping achieve better disease control;<sup>7</sup> either combination therapy inhibits interferon alpha, something which is not possible when using glucocorticoids on their own.<sup>8</sup> Furthermore, a synergistic/additive effect with cyclophosphamide, methotrexate, and cyclosporine-A has been described in patients with rheumatoid arthritis.<sup>9</sup> Growing evidence has been presented over the last two decades of the anti-inflammatory, anti-thrombotic, anti-hyperlipidemic capacity of these agents, leading to a second renaissance and wider use. The usefulness of antimalarials is discussed in several reviews considering various diseases.<sup>10,11</sup> The photoprotective property of these agents is another interesting feature that may explain their beneficial effects in photosensitive autoimmune diseases.<sup>12</sup> There are, however, still uncertainties about the real effectiveness of Qn and the most appropriate dosage. Therefore, in this study, we aimed to report our experience with photosensitive autoimmune diseases including LE and DM treated with Qn as either monotherapy or combination with other antimalarials, steroids, and immunosuppressive therapy in an add-on regimen in light of a review of the relevant literature.

## PATIENTS AND METHODS

Data were retrospectively collected from 38 patients (6 males, 32 females; mean age 45±8 years; range, 23 to 72 years) treated with Qn between March 2014 and June 2016 in the Autoimmune Diseases Unit of San Cecilio Hospital in Granada, Spain. The following data were obtained from the records of each patient: sex, age, diagnosis, duration of the disease, duration of treatment, smoking behavior, antimalarial treatment, concomitant treatment, and clinical indications, as well as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity before initiation, at the last visit, or when Qn treatment was completed. The patients were monitored every 12 weeks. At each visit, clinical data related to the patient's disease, side effects,

and adherence to the indicated treatment were recorded. The study protocol was approved by the San Cecilio Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We carried out a MEDLINE search for relevant articles, in any language, recorded between the inception of each database and December 30<sup>th</sup> 2016, using the Medical Subject Headings (MESH) categories: antimalarials, Qn, cutaneous lupus erythematosus (CLE), systemic lupus erythematosus (SLE), and DM. All cases identified from the literature were included in the analysis. All article references were reviewed to identify additional studies that were not included in the electronic databases. The data from these cases, together with the information from our patients, served as the basis of this report.

The clinical diagnosis of SLE was based on the American College of Rheumatology criteria.<sup>13</sup> The diagnosis of subacute cutaneous lupus erythematosus (SCLE) was defined according to Sontheimer,<sup>14</sup> and discoid lupus (DL) was based on clinical and histological data. DM was diagnosed according to the criteria of Bohan and Peter.<sup>15</sup>

To analyze the treatment response, we compared the SLEDAI in SLE<sup>16</sup> and the CLASI activity score<sup>17</sup> for CLE obtained at the visit prior to initiation of therapy with the score obtained at the final visit. The SLEDAI is a clinical index for assessing lupus disease activity. It consists of 24 weighted clinical and laboratory variables of nine organ systems. The descriptor scores range from 1 to 8, and the total possible score for all 24 descriptors is 105.

The CLASI scoring system has been developed specifically for patients with CLE, taking into account both the anatomical region (e.g., face, chest, arms) and morphological aspects of skin lesions. Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia. The total scores are calculated by simple addition based on the extent of the symptoms, which are documented according to the worst-affected lesion within a specific anatomical area. Treatment response in patients with DM was assessed by the physician based

**Table 1.** Clinical characteristics and therapy of our patients treated with quinacrine

Case	Diagnosis	Sex/Age (year)	Duration of disease (months)	Duration of treatment (months)	Smoker	Treatment	Concomitant treatment	Clinical indications	SLEDAI (E-L)	CLASI (E-L)	Side effects	Response
1	SLE+APS	F/45	270	19	Yes	100 Qn	CTC, AZA, MMF	Hydroxychloroquine intolerance	8→4			Yes
2	SLE+SCLE	F/39	24	42	No	50 Qn	CTC	Central serous chorioretinopathy	8→2	0→0		Yes
3	SLE	M/23	108	4	Yes	100 Qn	CTC	Optic neuritis	4→20			No
4	SLE+SCLE	F/61	96	16	History of smoking	100 Qn		Hydroxychloroquine Retinopathy	10→8	4→1	Yellow skin discoloration	Yes
5	SLE+DL	F/56	34	16	No	50 Qn	MTX	Itching induced by hydroxychloroquine	8→0	6→2		Yes
6	SLE+SCLE	F/43	174	135	History of smoking	50 Qn+HCQ	CTC	Disease activity	6→2	6→6		Yes
7	SLE+DL	F/47	86	84	No	50 Qn+HCQ	CTC	Disease activity	2→10	5→5		No
8	SLE+lupus panniculitis	F/40	147	12	No	100 Qn		Hydroxychloroquine intolerance	0→0	1→0		Yes
9	DL	F/42	58	7	Yes	100 Qn+HCQ	CTC, MTX,	Disease activity		6→0		Yes
10	DL	F/57	38	5	No	100 Qn+HCQ	CTC	Disease activity		4→3		Yes
11	DL	F/31	2	26	Yes	100 Qn+HCQ	MTX	Disease activity		2→2		No
12	SLE+SCLE	F/36	8	32	No	200 Qn+HCQ	CTC, MTX, efalizumab, MMF	Disease activity	12→4	4→8		Yes
13	SLE	F/44	24	20	No	50 Qn	CTC, MTX	Itching induced by hydroxychloroquine	0→2			Yes
14	SCLE	F/53	33	4	Yes	50 Qn+HCQ	CTC	Disease activity		4→0		Yes
15	DL+LP+SLE	F/54	9	101	Yes	50 Qn		Disease activity	6→0	6→0		Yes
16	SLE	F/31	7	77	No	50 Qn+HCQ	CTC, MTX	Disease activity	6→2			Yes
17	SLE	M/42	35	7	No	50 Qn		Itching induced by hydroxychloroquine	2→2			No
18	SLE	M/34	26	5	No	50 Qn	CTC, MMF	Hydroxychloroquine intolerance	4→2			Yes

**Table 1.** Continue

Case	Diagnosis	Sex/Age (year)	Duration of disease (months)	Duration of treatment (months)	Smoker	Treatment	Concomitant treatment	Clinical indications	SLEDAI (E-L)	CLASI (E-L)	Side effects	Response
19	SLE+Urticarial vasculitis	F/30	60	12	History of smoking	50 Qn+HCQ	CTC, MTX	Disease activity	4→6	4→4		No
20	Rowell's syndrome	F/57	15	12	No	100 Qn+HCQ	CTC	Disease activity	4→0	18→4		Yes
21	SLE+SCLÉ	F/45	12	6	No	50 Qn		Rash induced by hydroxychloroquine	0→0	2→0		Yes
22	SLE+Sjögren syndrome	F/66	228	7	No	50 Qn		Hydroxychloroquine retinopathy	3→3	6→6		No
23	SLE+DL+ Chilblains+ APS	F/44	141	15	No	100 Qn	MMF	Hydroxychloroquine intolerance	4→4	22→13		Yes
24	SLE+Chilblains	F/38	235	17	No	100 Qn+HCQ	MTX, Belimumab	Rash induced by hydroxychloroquine	0→0			NA
25	SLE+DM+ SE+Sjögren syndrome	F/72	147	18	No	50 Qn	CTC, Tacrolimus, MTX	Itching induced by hydroxychloroquine	12→2			Yes
26	SLE+Sjögren syndrome	F/31	58	17	No	100 Qn	MMF	Glaucoma	3→3			No
27	DL	M/34	37	9	Yes	100 Qn		Hydroxychloroquine intolerance	0→2			No
28	Chilblain lupus	M/70	105	13	No	50 Qn		Rash induced by hydroxychloroquine	8→10			No
29	SLE	F/56	116	21	Yes	50 Qn		Hydroxychloroquine retinopathy	7→0			Yes
30	LP+DL	F/39	96	18	Yes	100 Qn+HCQ	Thalidomide	Disease activity	4→2			Yes
31	SLE	F/55	22	22	No	50 Qn	CTC, AZA	Hydroxychloroquine retinopathy	1→0			Yes
32	DL	F/57	54	11	No	100 Qn		Hyperpigmentation by hydroxychloroquine	8→8	2→0		No
33	SLE	F/55	165	13	Yes	100 Qn	CTC, MMF	Digestive intolerance				Yes
34	SCLÉ	F/48	36	22	No	100 Qn	CTC, MTX	Retinopathy				Yes
35	DM	M/35	33	6	No	50 Qn+HCQ	CTC, AZA	Disease activity				Yes
36	DM	M/41	69	4	No	100 Qn+HCQ	CTC, AZA, RTX	Disease activity				Yes
37	DM	F/43	83	1	No	100 Qn +HCQ	CTC	Disease activity				No
38	DM+DL	F/48	2	1	No	100 Qn		Hydroxychloroquine retinopathy	6→6		Itching	No

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; E-L: Early-late; SLE: Systemic lupus erythematosus; APS: Antiphospholipid syndrome; Qn: Quinacrine; CTC: Corticosteroids; AZA: Azathioprine; MMF: Mycophenolate mofetil; SCLÉ: Subacute cutaneous lupus erythematosus; DL: Discoid lupus; MTX: Methotrexate; HCQ: Hydroxychloroquine; SE: Systemic sclerosis; LP: Lupus panniculitis; DM: Dermatomyositis; RTX: Rituximab; NA: Not applicable.

on the improvement in the extent of the disease (number of lesions, affected surface area, and activity of the disease), as expressed in erythema and pruritus. Qn was stopped in patients with unsatisfactory effects, or if a response was not deemed adequate.

Quinacrine was obtained from Normon laboratories (Tres Cantos, Madrid, Spain).

Off-label Qn use was requested for each patient. Qn was administered as an add-on regimen therapy in a minimal effective dose regimen if the patients had not responded to other antimalarial or corticosteroids and/or other immunosuppressors previously. If a patient had a different Qn dose regimen, the highest dose was considered for the study.

**Table 2.** Patient characteristics

	Literature			Present report		
	n	%	Mean±SD	n	%	Mean±SD
No of patients	188			38		
Age (year)			41.4±12.8			45.8±11.6
Female	129	68.6		32	84.2	
Diagnosis						
Systemic lupus erythematosus	60	31.9		24	63.2	
Discoid lupus	88	46.8		11	28.9	
Subacute cutaneous lupus erythematosus	31	16.5		7	18.4	
Acute lupus	10	5.3		0	0	
Chilblain	4	2.1		3	7.9	
Panniculitis (lupus profundus)	9	4.8		3	7.9	
Chronic lupus	5	2.6		0	0	
Skin lesions	3	1.6		0	0	
Lupus tumidus	19	10.1		0	0	
Hypertrophic lupus	1	0.5		0	0	
Urticaria	0	0		1	2.6	
Rowell	0	0		1	2.6	
Dermatomyositis	14	7.4		4	10.5	
Disease duration in months			120.1±100			76.1±69.5
Follow-up duration therapy in months			30.3±32.7			22.6±28.9
Quinacrine dosage (mg/day)						
50	5	2.6		18	47.4	
100	127	67.5		19	10.3	
150	1	0.5		0	0	
200	18	9.6		1	2.6	
300	12	6.4		0	0	
100-300	25	13.3		0	0	
Concomitant therapy with Qn						
CTC	63	33.5		21	55.3	
Hydroxychloroquine	108	57.4		16	42.1	
Cloroquine	36	19.1		0	0	
Methotrexate	14	7.4		10	26.3	
Azatioprine	6	3.2		4	10.5	
Mycophenolate mofetil	1	0.5		6	15.8	
Thalidomide	2	1.1		1	2.6	
Intravenous immunoglobulins	1	0.5		0	0	
Rituximab	0	0		1	2.6	
Tacrolimus	0	0		1	2.6	
Belimumab	0	0		1	2.6	
Efalizumab	0	0		1	2.6	
Azatioprine, mycophenolate mofetil or cyclosporine	8	4.3		0	0	
Response						
Yes	132	70.2		25	68.4	
No	54	28.7		11	28.9	
Not applicable	2	1.1		1	2.6	

SD: Standard deviation; Qn: Quinacrine; CTC: Corticosteroids.

**Table 3.** Adverse events

	Literature (n=188)	This study (n=38)
Yellow skin discoloration	26	1
Drug rash	3	
Dermatitis	2	
Psoriasis	1	
Photosensitivity	1	
Itching	1	1
Stroke	1	
Nausea	2	
Hepatitis	2	
Epigastralgia	1	
Fatigue	1	
Weight loss	1	

## RESULTS

Patient demographics were provided in Table 1a. Of the 38 patients, 34 were suffering from SLE or cutaneous lupus. Of the 24 patients with SLE, Qn treatment was started due to skin disease in seven and disease activity in the others. Eleven patients had DL, seven had SCLE, three had chilblain lupus, three had lupus panniculitis, one had urticaria, and one had Rowell's syndrome. Only four patients had DM.

Quinacrine was dosed at 50 or 100 mg in most of the patients and the mean follow-up was  $22.6 \pm 28.9$  months. In our series, one patient received 200 mg/day, 19 patients 100 mg/day, and 18 patients 50 mg/day. Qn was combined with HCQ in 16 patients. Twenty-seven patients had Qn as an add-on regimen therapy, most with steroids (n=21), followed by methotrexate in 10 patients, mycophenolate in six patients, and azathioprine in four patients.

The most frequent clinical indications were disease activity (36.8%), followed by retinopathy (18.42%), HCQ intolerance (itching, cutaneous rash or digestive intolerance) (15.8%) and others.

Clinical response was analyzed in patients with SLE or cutaneous lupus. Responders were patients who improved their SLEDAI or CLASI activity. Twenty-five patients were responders (68.4%), 13 (52%) improved their CLASI activity and 12 (48%) their SLEDAI. The median change

in SLEDAI was  $1.25 \pm 5.4$ . No response (lack of treatment efficacy) was observed in four patients with SLE, two patients with DL, one patient with SLE and DL, one patient with SLE and urticarial vasculitis, and another patient with SLE, DL, and chilblains.

The indication for use of Qn in patients with DM was cutaneous disease, with 50% of patients responding. Altogether for lupus and DM, the response rate was 56% with Qn alone and 73.3% when Qn was combined with HCQ. In patients who received 50 mg/day, the response rate was 72%, with 100 mg/day 63.2%, and with 200 mg/day 100% (single patient).

A total of 188 cases were identified in the literature (Table 1b),<sup>6,7,11,18-25</sup> of which 129 were females; the mean age was  $41.4 \pm 12.8$  years (standard deviation) with a disease duration of  $76.2 \pm 96.3$  months.

The most frequent diagnosis was cutaneous lupus (68.6%), followed by SLE (32.6%). Only 7.4% of patients had DM. Most patients received concomitant medication, predominantly steroids (33.5%) and other types of antimalarials. Fourteen patients received methotrexate and six azathioprine. Most patients were treated using Qn with HCQ (55.3%) or CQ (17.5%).

The mean duration of therapy was  $30.3 \pm 32.7$  months. A high percentage of patients responded well to the treatment (Table 2). Treatment response was 73% in patients with SLE or cutaneous lupus. No response was seen in two patients with SLE, 14 patients with DL, eight patients with tumid lupus (TL), four patients with SCLE, three patients with DL and SLE, one with SLE and acute cutaneous lupus (ACL), one with TL and DL, one with SLE and SCLE, one with ACL and lupus panniculitis (LP), and another with SLE and DL and TL. Cavazzana et al.<sup>18</sup> reported that SCLE lesions improved in 60% of cases, without a significant decrease in the activity. In addition, all acute lupus rashes and 50% of chilblains improved during therapy. In contrast, lupus panniculitis (lupus profundus) showed no amelioration.

In patients with DM, the treatment response was 35.7% as indicated clinically by cutaneous symptoms. Most patients had more than one antimalarial as an add-on regimen.



Altogether for lupus and DM, 85.1% of the patients responded to Qn on its own, 68.3% to Qn and HCQ, and 59.4% to Qn and CQ. In four patients, a triple therapy was used (HCQ with Qn and CQ), but only one responded to treatment. The most frequent dose administered was 100 mg. Among the patients who responded, treatment response with Qn alone or in combination was 91.67%, 84%, 83.3%, 68.5%, 100%, and 80% for patients taking 300, 300-100, 200, 100, 150 and 50 mg/day, respectively. Side effects were scarce; one patient had yellow skin discoloration while another experienced itching (Table 3).

## DISCUSSION

Assuming that part of the antimalarial effect is due to the photoprotective effect, the aim of this study was to analyze the effectiveness of Qn, both alone or in combination with other antimalarials or immunosuppressive therapy, as an add-on regimen therapy for patients with photosensitive conditions, such as cutaneous lupus, SLE, and DM.

A high response rate to Qn treatment was observed both among our patients and those reported in the reviewed literature (68.4% and 70.2%, respectively). The best response rate was observed in patients suffering from SLE or cutaneous lupus.

In cases of cutaneous lupus, the treatment may be used for patients with DL, SCLE, lupus panniculitis (lupus profundus), TL, hypertrophic lupus and chilblains. Although Cavazzana et al.<sup>18</sup> reported that the therapy did not benefit patients with lupus profundus, we observed a good response in such patients; Feldmann et al.<sup>26</sup> found that skin lesions improved significantly or cleared totally in all SCLE and half of chronic LE patients; and Lipsker et al.<sup>6</sup> found that three-quarters of DL, all SCLE, and all DL/SCLE patients demonstrated between 50% and total clearance of lesions. As in most patients in the literature, we observed higher response in patients with DL and SCLE. We also noted the benefit of this therapy for urticaria and Rowell's syndrome. However, no response was observed in urticaria vasculitis sufferers.

In most of our patients with SLE, we observed improved SLEDAI score. In two cases (Cases 6 and 12), there was improved SLEDAI even though there was no change in CLASI score. However, Cases 17, 19 and 29 did not respond at all. Case 19 needed other immunosuppressive therapy while Cases 17 and 29 remained stable. Numerous systemic treatments were proposed for these patients, including mycophenolate mofetil, methotrexate, dapsone, thalidomide, intravenous immunoglobulin and biologicals; antimalarials were used as an add-on regimen. Similar to Toubi et al.,<sup>7</sup> we observed a corticosteroid-sparing effect with the combination therapy in this group of patients. Taken together, these studies provide evidence supporting the use of Qn for treating lupus patients.

The pathophysiology of photosensitive autoimmune skin reactions could be explained by ultraviolet (UV)-induced production of tumor necrosis factor alpha secretion that leads to keratinocyte apoptosis and the translocation of previously sequestered cellular antigens that then activate the immune system.<sup>27</sup> Several explanations have been given for the effectiveness of antimalarials in inhibiting SLE activity, including lysosomal stabilization; inhibition of antigen presentation and cell-mediated cytotoxicity; inhibition of prostaglandin synthesis; inhibition of lipid peroxidation; inhibition of proinflammatory cytokine synthesis; influence on apoptosis, reduction of the levels of circulating immune complexes; antioxidant action, antithrombotic/antiplatelet effects;<sup>8,28</sup> and photoprotective effects.<sup>12</sup> It has been shown that the accumulation of antimalarials in the skin exerts a local anti-inflammatory effect after ultraviolet-B (UV-B) exposure,<sup>29</sup> which could explain the benefit of this drug in conditions associated with photosensitivity.<sup>30</sup>

Antimalarials have also been used for treating cutaneous symptoms of DM since at least 1984, after Woo et al.<sup>31</sup> reported their successful use in this condition; however, the response rate was lower than that seen in patients with lupus. In our series, when considering the diseases individually, the responses were also worse in patients with DM compared with those in patients with lupus. To date, the response rates in this study are higher than those reported in the literature.<sup>11</sup> DM patients, similar to those with LE, show

significantly increased erythematous sensitivity to UV-B irradiation,<sup>27</sup> while Qn seems less effective in treating the cutaneous symptoms of these patients. The high proportion of patients with DM that responded well in our series is probably due to the low number of patients. As in the previously published studies, most of our patients received glucocorticoids concomitantly with immunosuppressive agents.

In our patients, the best response was seen with the combination of Qn and HCQ. In most patients, this combination was not used due to intolerance or contraindication for the use of HCQ; if the association had been possible, it is likely that the response rate would have been higher. Qn can be an alternative treatment for patients who respond poorly or are intolerant to HCQ, although antimalarials, when combined, may exert a complementary effect, thus explaining the enhanced efficacy observed with the combination therapy. We did not treat our patients with the HCQ and CQ combination as it can increase ocular toxicity and is therefore not recommendable. Chang et al.<sup>25</sup> reported improvement in 67% of their patients treated with a combination of HCQ and Qn, and 33% of their cases treated with a combination of CQ and Qn. The combined therapy could be effective not only in patients with photosensitivity, but also in those who are not suffering this condition. This type of therapy could induce remission in patients with long-lasting disease activity and severe systemic involvement of major organs; this may be associated with a significant corticosteroid-sparing effect.

With regard to dose, data from the literature indicate the use of Qn at between 300 mg/day and 50 mg/day. In the study of Rhodes and Allende,<sup>20</sup> dosage concentration was from 100-300 mg/day; however, the number of patients treated with 100 mg/day or 300 mg/day was unclear.

In the study carried out by Carvazzana et al.,<sup>18</sup> treatment with 100 mg/day and 50 mg/day provided the same response rate. On the other hand, patients taking 100 mg/day of Qn presented significantly faster improvement than those taking 50 mg/day and a reduced steroid dosage. It would probably be advisable to start treatment at 100 mg/day and continue with 50 mg/day maintenance doses. It is, however,

necessary to find the optimum dose for each patient, balancing the toxic effects and a clinically relevant response.

Yellow staining of the skin is a minor side effect of Qn use, although possible bone-marrow and/or nephrotoxic manifestations have been reported elsewhere.<sup>32</sup> In both our patients and those collected from the literature, no serious side effects were observed during the follow-up period (of up to 30 years), with the exception of a case of severe hepatitis in a patient affected by SLE and chronic hepatitis C virus (HCV) infection.<sup>18</sup> The liver histology of this patient showed double damage, caused by aggressive hepatitis with piecemeal necrosis (due to chronic HCV hepatitis), and drug-induced-damage, represented by cholangiolitis and microinfarcts in portal spaces. Cavazzana et al.<sup>18</sup> reported side effects in patients receiving 100 mg/day, while none in patients receiving 50 mg/day.

There are several limitations to our study. Firstly, this is not a clinical trial. Secondly, it includes patients with heterogeneous characteristics and a small sample size. However, this is a study with real-life conditions and it is striking that the responses observed in our patients are similar to those reported in the literature. We believe that this is an argument in favor of our results' consistency.

In conclusion, Qn (as an "off-label drug") can be useful in three clinical situations: (i) to avoid antimalarial ocular toxicity in patients with HCQ retinopathy or another ocular disease; (ii) to allow the use of antimalarials when other antimalarials are not tolerated (itching, rash due to HCQ, or digestive intolerance); and (iii) to improve a sub-optimal antimalarial response as an add-on therapy. Combining this therapy with other antimalarials can help control the activity of photosensitive autoimmune diseases, particularly SLE. Larger studies are necessary to evaluate the response to antimalarials and any differences across cutaneous subtypes. Further studies are also required to assess the optimal treatment regimen in different subsets, as well as treatment dosage and combinations.

#### **Declaration of conflicting interests**

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