

ONLINE FIRST

Response to Antimalarial Agents in Cutaneous Lupus Erythematosus

A Prospective Analysis

Aileen Y. Chang, BA; Evan W. Piette, MD; Kristen P. Foering, MD; Thomas R. Tenhave, PhD, MPH; Joyce Okawa, RN; Victoria P. Werth, MD

Objective: To demonstrate response to antimalarial agents in patients with cutaneous lupus erythematosus (CLE) using activity scores from the Cutaneous Lupus Erythematosus Disease Area and Severity Index, a validated outcome measure.

Design: Prospective, longitudinal cohort study.

Setting: University cutaneous autoimmune disease clinic.

Participants: A total of 128 patients with CLE who presented from January 2007 to July 2010 and had at least 2 visits with activity scores.

Intervention: Administration of antimalarial agents.

Main Outcome Measures: Response was defined by a 4-point or 20% decrease in activity score. Response to initiation was determined by the difference between the scores before treatment and at the first visit at least 2 months after treatment. Response to continuation was determined by the difference between the scores at the first visit and the most recent visit while undergoing treatment.

Results: Of 11 patients who initiated treatment with hy-

droxychloroquine, 55% were responders (n=6), showing a decrease in median (interquartile range [IQR]) activity score from 8.0 (3.5-13.0) to 3.0 (1.8-7.3) (P=.03). Of 15 patients for whom hydroxychloroquine failed, 67% were responders to initiation of hydroxychloroquine-quinacrine therapy (n=10), showing a decrease in median (IQR) activity score from 6.0 (4.8-8.3) to 3.0 (0.75-5.0) (P=.004). Nine of 21 patients who continued hydroxychloroquine treatment (43%), and 9 of 21 patients who continued hydroxychloroquine-quinacrine (43%) were responders, showing a decrease in median (IQR) activity score from 6.0 (1.5-9.5) to 1.0 (0.0-4.5) (P=.01) and 8.5 (4.25-17.5) to 5.0 (0.5-11.5) (P=.01), respectively.

Conclusions: The use of quinacrine with hydroxychloroquine is associated with response in patients for whom hydroxychloroquine monotherapy fails. Further reduction in disease activity can be associated with continuation of treatment with antimalarial agents.

Arch Dermatol. 2011;147(11):1261-1267.

Published online July 18, 2011.

doi:10.1001/archdermatol.2011.191

Author Affiliations:

Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania (Mss Chang and Okawa and Drs Piette, Foering, and Werth); Department of Dermatology (Mss Chang and Okawa, and Drs Piette, Foering, and Werth), Institute for Translational Medicine and Therapeutics (Dr Foering), and Center for Clinical Epidemiology and Biostatistics (Dr Tenhave), University of Pennsylvania, Philadelphia.

ANTIMALARIAL DRUGS HAVE been in use for the treatment of cutaneous lupus erythematosus (CLE) since 1894, when the use of quinine was reported to be beneficial in lupus erythematosus (LE).¹ During World War II,

See Practice Gaps at end of article

British physicians observed that soldiers with rheumatoid arthritis and systemic lupus erythematosus (SLE) improved while taking quinacrine, a synthetic derivative of quinine.² Following the landmark 1951 article by Page,³ various reports over the next

10 years confirmed the efficacy of antimalarial agents in treating LE.⁴ Antimalarial agents are now considered first-line systemic therapy in CLE.^{5,6} Several mechanisms have been proposed to explain the



CME available online at www.jamaarchivescme.com

therapeutic benefit of antimalarial agents in CLE: suppression of antigen presentation, inhibition of prostaglandin and cytokine synthesis, lysosomal stabilization, inhibition of toll-like receptor signaling, and photoprotective properties.^{7,8}

Currently, the antimalarial agents used to treat CLE include hydroxychloro-

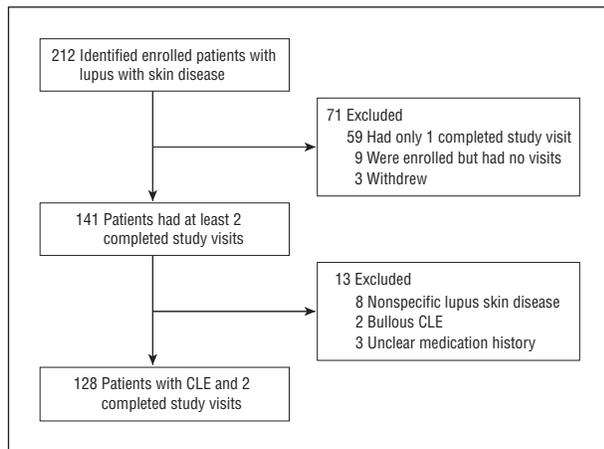


Figure 1. Identification of the 128 study patients. CLE, indicates cutaneous lupus erythematosus.

quine, chloroquine, and quinacrine.⁶ There have been 2 randomized controlled trials demonstrating improvement in patients taking hydroxychloroquine or chloroquine, though neither was placebo controlled.^{9,10} These data are supported by numerous case reports and case series.¹¹ Although quinacrine was the first synthetic antimalarial agent reported as beneficial in treating LE, its use declined as hydroxychloroquine was believed to be safer and to have fewer side effects. Only in the past 20 years has there been a renewed interest in quinacrine.¹² Response to quinacrine, in combination with either hydroxychloroquine or chloroquine, has been documented in the treatment of CLE, with response determined by unvalidated clinical criteria and an unvalidated use of a CLE-specific outcome measure.¹³⁻¹⁵ It has also been documented in the treatment of SLE with an SLE-specific outcome measure.¹⁶

There are few studies that systemically evaluate the use of medications, including antimalarial agents, in treating CLE.¹⁷ The purpose of the present study was to demonstrate prospectively the response to antimalarial monotherapy and combination therapy in a cohort of patients with CLE using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI),¹⁸ a disease-specific outcome measure.

METHODS

IDENTIFICATION OF PATIENTS

This is a prospective, longitudinal cohort study of patients with CLE. Using our ongoing database of patients with LE with skin manifestations,¹⁹ we identified 212 patients with CLE or SLE with nonspecific lupus skin disease who were enrolled in the database between January 5, 2007, and July 9, 2010. We included patients with diagnoses of chronic (CCLE), subacute (SCLE), and acute (ACLE) subtypes of CLE, based on the modified Gilliam classification.²⁰ We also included patients diagnosed as having SLE, based on American College of Rheumatology revised criteria.²¹ We excluded patients with nonspecific lupus skin findings, bullous ACLE (blisters are not captured by the CLASI), or unclear medication history (eg, medications taken intermittently). **Figure 1** demonstrates how we identified eligible patients for this study.

From the 128 eligible patients, we identified those who initiated and/or continued the following antimalarial therapies: hydroxychloroquine, hydroxychloroquine-quinacrine, chloroquine, and chloroquine-quinacrine. We excluded patients who were taking concomitant nonantimalarial immunomodulators, such as dapsone and thalidomide, or concomitant immunosuppressive drugs, such as corticosteroids, methotrexate, mycophenolate, azathioprine, cyclophosphamide, cyclosporine, and rituximab. We included patients who were using concomitant topical or intralesional medications.

This study was approved by our institutional review board (IRB). All subjects were enrolled after having signed the IRB-approved written informed consent and the Health Insurance Portability and Accountability Act authorization.

TREATMENT PROTOCOL

Hydroxychloroquine was dosed at 200 mg/d to 400 mg/d, based on ideal body weight. Chloroquine was dosed at 250 mg/d for 5 to 7 days/wk, determined by ideal body weight. Quinacrine was dosed at 100 mg/d. In our clinic, we use an algorithmic approach for antimalarial therapy.⁶ If first-line hydroxychloroquine treatment fails, we add quinacrine. If hydroxychloroquine-quinacrine treatment has previously failed or the patient does not have access to a compounding pharmacy, we consider the use of chloroquine. We use chloroquine-quinacrine if the hydroxychloroquine-quinacrine or chloroquine treatment fails.

CLASI MEASUREMENT TOOL

The CLASI¹⁸ is a validated clinical tool that quantifies disease activity and damage in patients with CLE. The activity score is based on the degree of erythema, scale, mucous membrane lesions, and nonscarring alopecia.¹⁸ The CLASI has been shown to have good content validity as well as interrater and intrarater reliability. Since its development, the CLASI has been used in several studies that have examined all subsets of CLE.^{13,22-27}

Recent work has demonstrated that a 4-point or 20% decrease in CLASI activity score is the most specific criterion for classifying patients as responders or nonresponders and represents the minimal clinically important change.²⁸ *Responders* are patients who have improved. *Nonresponders* are patients who have not improved, defined as either unchanged or worsened. *Disease severity* is defined by the following CLASI activity score criteria: mild, 0-9; moderate, 10-20; and severe, 21-70.²⁸ To calculate percentage change when the baseline CLASI activity score (ie, the denominator value) was zero, we added 0.5 points to each score to allow the percentage change to be calculated. This is consistent with previous methods.²⁸

TREATMENT RESPONSE ANALYSIS

For the initiation-of-treatment analysis, we compared the CLASI activity score obtained at the visit before initiation of therapy with the score obtained at the first follow-up visit after initiation. The first follow-up visit occurred at least 2 months after initiation, based on clinical practice and data indicating that antimalarial agents may take up to 2 months to demonstrate benefit.⁶ Based on the change and percentage change in CLASI score between the visit prior to initiation and the first follow-up visit after initiation, we categorized patients as responders (improved) or nonresponders (unchanged or worsened) using the criteria of 4-point or 20% decrease in CLASI activity score.²⁸

For the continuation-of-treatment analysis, we compared the CLASI activity score obtained at the first visit while under-

Table 1. Characteristics of Responders and Nonresponders at Initiation of Treatment^a

Tx	Group ^b	Patients, No. (%)	Age, Mean (SD), y	Male Sex, No.	Smokers, No.	Diagnoses
HCQ	All	11 (100)	49 (15)	1	1	See responder/nonresponder category
	R	6 (55)	48 (17)	1	1 ^c	1 Localized DLE, 1 generalized DLE/LP, 2 tumid LE, 2 SCLE
	NR	5 (45)	49 (14)	0	0	1 Localized DLE, 1 generalized DLE, 1 tumid LE, 1 chilblains lupus, 1 SLE/localized DLE
HCQ-Qn	All	15 (100)	46 (13)	4	6	See responder/nonresponder category
	R	10 (66)	46 (14)	2	4	2 Localized DLE, 1 localized DLE/LP, 1 generalized DLE, 4 tumid LE, 1 SCLE, 1 SLE with localized DLE, LP, and hypertrophic LE
	NR	5 (33)	45 (13)	2	2	2 Tumid LE, 1 generalized DLE, 1 SCLE, 1 SLE/ACLE
CQ	All R	3 (100)	47 (18)	0	3	1 SCLE, 1 localized DLE, 1 SLE/SCLE/ACLE
CQ-Qn	All	6 (100)	41 (14)	1	2	See responder/nonresponder category
	R	2 (33)	42 (25)	1	0	1 SCLE, 1SLE/SCLE/ACLE
	NR	4 (67)	40 (10)	0	2 ^c	1 Localized DLE, 1 tumid LE, 1 tumid LE/generalized DLE, 1 SLE/SCLE

Abbreviations: ACLE, acute cutaneous LE; CQ, chloroquine; DLE, discoid LE; HCQ, hydroxychloroquine; LE, lupus erythematosus; LP, lupus panniculitis; NR, nonresponders; Qn, quinacrine; R, responders; SCLE, subacute cutaneous LE; SD, standard deviation; SLE, systemic LE; Tx, treatment.

^aThere was no difference in age, sex, and number of smokers between responders and nonresponders in each treatment group.

^bResponse status at first follow-up visit after initiation.

^cOne patient quit smoking between visits.

going therapy with the score obtained at the most recent visit while undergoing therapy and categorized patients into responders or nonresponders. For patients who initiated treatment while in the study, we also looked at their initial responsiveness to the treatment.

Not all patients who initiated treatment were included in the continuation-of-treatment analysis, for several reasons: lost to follow-up (defined as no visit in over a year), follow-up visit had not occurred yet, or medication change. Likewise, not all patients included in the continuation-of-treatment analysis were included in the initiation-of-treatment analysis because some patients started treatment prior to enrollment in the database.

STATISTICAL ANALYSIS

The CLASI scores were not normally distributed. Age and duration between visits were normally distributed. We used Wilcoxon signed rank tests to compare CLASI scores between visits for all patients, responders, and nonresponders within each treatment group. We did not adjust for multiple comparisons because this analysis was exploratory. With this strategy, we avoided being too conservative and hence missing important exploratory findings.²⁹ Between responders and nonresponders within each treatment group, we used *t*-tests to compare age and duration between visits and Fisher exact tests to compare sex and smokers. Stata software, version 11.0 (StataCorp LP, College Station, Texas) was used for data analysis. GraphPad Prism, version 5.0 (GraphPad Software Inc, La Jolla, California) was used for data analysis and graph making.

RESULTS

PATIENT CHARACTERISTICS

Characteristics of patients who initiated each therapy, as well as comparisons between responders and nonresponders, can be found in **Table 1**. Similar statistics for

patients who continued each therapy can be found in **Table 2**.

INITIATION OF HYDROXYCHLOROQUINE MONOTHERAPY

Eleven patients, representing 8.6% of the study population (11 of 128), initiated hydroxychloroquine therapy while enrolled in the database. These patients had either been untreated, or topical and/or intralesional treatments had failed. Six of these 11 patients were responders, showing a decrease in median (interquartile range [IQR]) CLASI activity score from 8.0 (3.5-13.0) to 3.0 (1.8-7.3) from treatment initiation to the first follow-up visit ($P = .03$) (**Figure 2A**). Five of the 11 patients were nonresponders, showing an increase in median (IQR) CLASI score from 3.0 (1.5-6.5) to 5.0 (4.5-8.0) from treatment initiation to the first follow-up visit ($P = .10$) (**Figure 2B**).

CONTINUATION OF HYDROXYCHLOROQUINE MONOTHERAPY

Twenty-one of 128 patients, representing 16% of the study population, had at least 2 consecutive visits while being treated with hydroxychloroquine. Half of these had been undergoing hydroxychloroquine treatment for over 12 months ($n = 11$). Nine of the 21 patients were responders, continuing hydroxychloroquine treatment over a mean (IQR) duration of 9.2 (3.3-13.0) months (**Figure 3A**). Twelve of the 21 patients were nonresponders, continuing hydroxychloroquine treatment over a mean (IQR) duration of 14 (2.8-26) months (**Figure 3A**). Of these 12 patients, 5 required the addition of quinacrine to their antimalarial regimen. Continuation data for patients who initiated hydroxychloroquine therapy while enrolled in the database are shown in **Figure 2**.

Table 2. Characteristics of Responders and Nonresponders With Continuation of Treatment^a

Tx	Group ^b	Patients, No. (%)	Age, Mean (SD), y	Male Sex, No.	Smokers, No.	Diagnoses
HCQ	All	21 (100)	51 (14)	3	6	See responder/nonresponder category
	R	9 (43)	54 (17)	1	1	4 SCLE, 2 tumid LE, 1 tumid/ACLE, 1 localized ACLE/SLE, 1 SLE with localized DLE/ACLE
	NR	12 (57)	49 (12)	2	5	1 SCLE, 1 generalized DLE, 4 localized DLE, 4 tumid LE, 1 LP, 1 SLE with localized DLE, LP, and hypertrophic LE
HCQ-Qn	All	21 (100)	48 (12)	7	9	See responder/nonresponder category
	R	9 (43)	47 (12)	4	4	2 SCLE, 2 localized DLE, 3 generalized DLE, 2 tumid LE
	NR	12 (57)	49 (13)	3	5	1 SCLE, 2 localized DLE, 3 generalized DLE, 4 tumid LE, 1 localized LE/LP, 1 SLE with localized DLE/tumid LE
CQ	All NR	3 (100)	49 (20)	0	1 ^c	1 localized DLE, 1 SCLE, 1 tumid LE
CQ-Qn	All	5 (100)	49 (13)	1	3	See responder/nonresponder category
	R	1 (20)	45 (8)	0	1	1 Generalized DLE/tumid LE
	NR	4 (80)	51 (9)	0	2	2 Localized DLE, 1 SCLE, 1 tumid LE

Abbreviations: ACLE, acute cutaneous LE; CQ, chloroquine; DLE, discoid LE; HCQ, hydroxychloroquine; LE, lupus erythematosus; LP, lupus panniculitis; NR, nonresponders; Qn, quinacrine; R, responders; SCLE, subacute cutaneous LE; SD, standard deviation; SLE, systemic LE; Tx, treatment.

^aThere was no difference in age, sex, and number of smokers between responders and nonresponders in each treatment group.

^bResponse status at most recent visit on treatment.

^cQuit smoking between first visit and most recent visit while undergoing treatment.

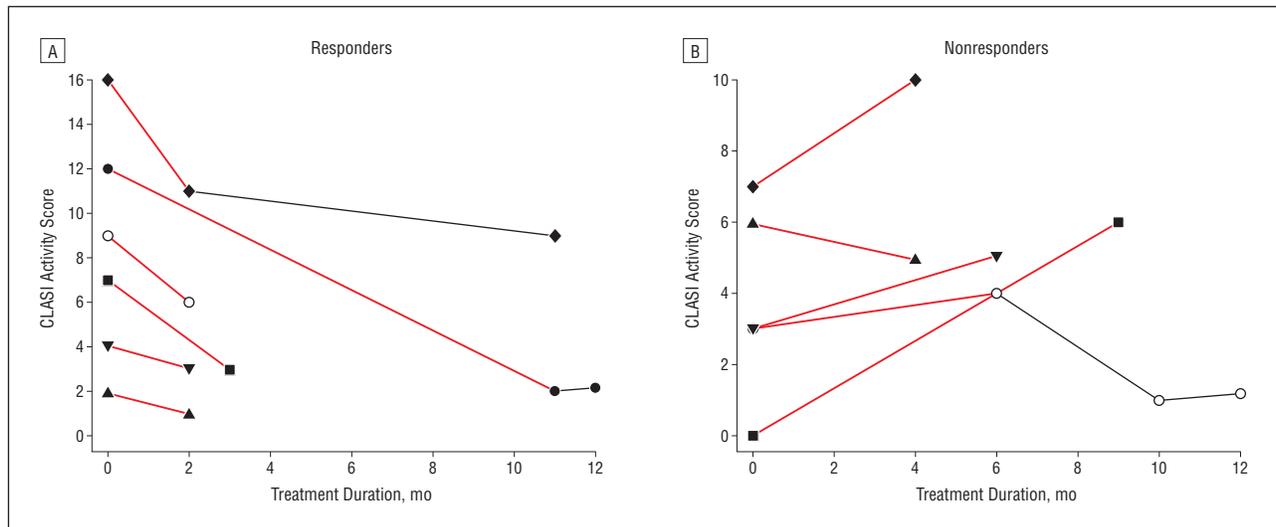


Figure 2. Hydroxychloroquine initiation at month 0. A, 6 patients were responders at first follow-up visit (55%). B, 5 patients were nonresponders at first follow-up visit (45%). Initiation data are shown in red. CLASI indicates Cutaneous Lupus Erythematosus Disease Area and Severity Index.¹⁸

INITIATION OF HYDROXYCHLOROQUINE-QUINACRINE THERAPY

Fifteen of the 128 patients, representing 12% of the study population, initiated hydroxychloroquine-quinacrine therapy while enrolled in the database. These patients were either currently taking hydroxychloroquine, or hydroxychloroquine treatment had failed for them in the past. Ten of these 15 patients were responders, showing a decrease in median (IQR) CLASI activity score from 6.0 (4.8-8.3) to 3.0 (0.75-5.0) from treatment initiation to the first follow-up visit ($P=.004$) (Figure 4A). Five of the 15 patients were nonresponders, showing a decrease in median (IQR) CLASI activity score from 9.0 (3.5-24.0) to 8.0 (3.0-23.0) from

treatment initiation to the first follow-up visit ($P=.27$) (Figure 4B).

CONTINUATION OF HYDROXYCHLOROQUINE-QUINACRINE THERAPY

Twenty-one of the 128 patients, representing 16% of the study population, had at least 2 consecutive visits while being treated with hydroxychloroquine-quinacrine. Twenty-five percent of these patients had been undergoing hydroxychloroquine-quinacrine treatment for over 12 months ($n=5$). Nine of the 21 patients were responders with continuation of hydroxychloroquine-quinacrine treatment over a mean (IQR) duration of 9.0 (4.0-13.0) months (Figure 3B). Twelve of the 21 pa-

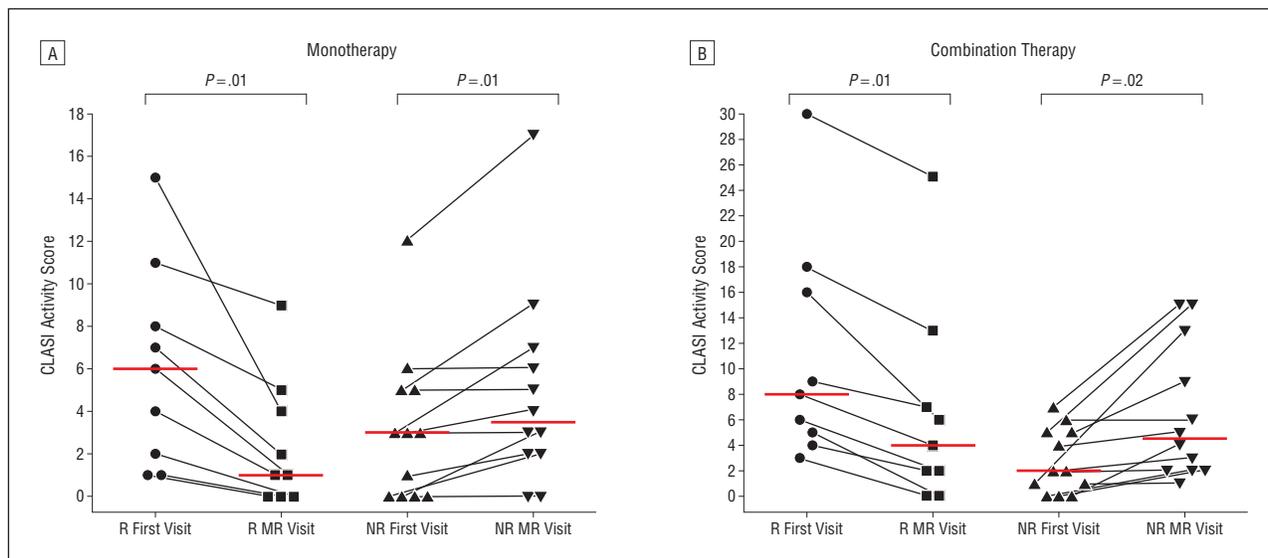


Figure 3. Continuation of treatment with antimalarial hydroxychloroquine monotherapy (A) and hydroxychloroquine-quinacrine combination therapy (B). Shown are the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)¹⁸ activity scores at first visit and most recent (MR) visit while undergoing treatment. Median CLASI scores are shown in red. NR indicates nonresponders; R, responders.

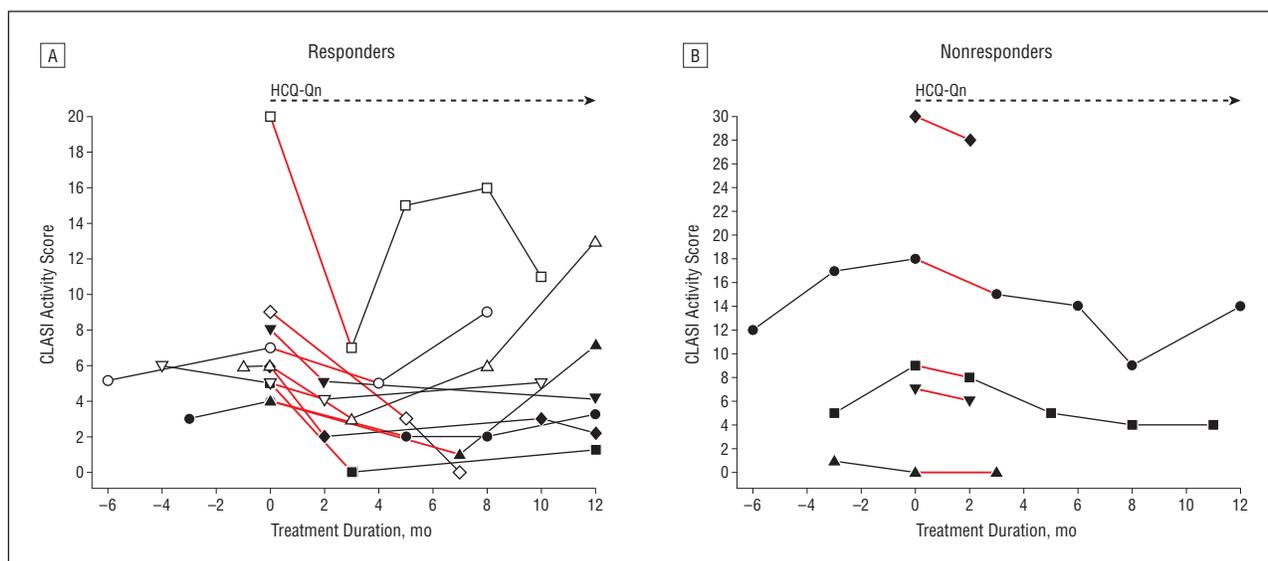


Figure 4. Hydroxychloroquine-quinacrine (HCQ-Qn) initiation at month 0. A, Ten patients (two-thirds) were responders at the first follow-up visit. B, Five patients (one-third) were nonresponders at the first follow-up visit. Initiation data are shown in red. CLASI indicates Cutaneous Lupus Erythematosus Disease Area and Severity Index.¹⁸

tients were nonresponders with continuation of hydroxychloroquine-quinacrine over a mean (IQR) duration of 15.0 (7.6-21.0) months (Figure 3B). Of these 12 patients, 3 patients required a medication change, either switching from hydroxychloroquine-quinacrine to chloroquine-quinacrine or adding an immunosuppressive agent. Continuation data for patients who initiated hydroxychloroquine-quinacrine therapy while enrolled in the database are shown in Figure 4.

INITIATION OF CHLOROQUINE MONOTHERAPY

Three of 128 patients, representing 2.3% of the study population, initiated chloroquine therapy while en-

rolled in the database. Treatment with hydroxychloroquine had failed for all 3, and hydroxychloroquine-quinacrine therapy had failed for 1. All 3 patients were responders (Table 1).

CONTINUATION OF CHLOROQUINE MONOTHERAPY

Three of 128 patients, representing 2.3% of the study population, had at least 2 consecutive visits while undergoing chloroquine treatment. All were nonresponders with continuation of chloroquine over a mean (IQR) duration of 15.0 (6.1-30.0) months (Table 2). Two patients required the addition of quinacrine to their antimalarial regimen.

INITIATION OF CHLOROQUINE-QUINACRINE THERAPY

Six of 128 patients, representing 4.7% of the study population, initiated chloroquine-quinacrine treatment while enrolled in the database. Hydroxychloroquine and hydroxychloroquine-quinacrine therapy had failed for all 6 patients. Two of the 6 patients were responders (Table 1).

CONTINUATION OF CHLOROQUINE-QUINACRINE THERAPY

Five of 128 patients, representing 3.9% of the study population, had at least 2 consecutive visits while undergoing chloroquine-quinacrine treatment. One of these 5 was a responder with continuation of chloroquine-quinacrine treatment over 12 months (Table 2). Four of the 5 patients were nonresponders with continuation of chloroquine-quinacrine therapy over a mean (IQR) duration of 18.0 (3.4-35.0) months. Of these 4 patients, 1 required the addition of thalidomide to the treatment regimen.

COMMENT

Our prospective analysis presents evidence of response to antimalarial agents, without concomitant immunosuppressive or immunomodulator use, in a CLE population seen at an academic referral center. In our patients who initiated hydroxychloroquine therapy, about half demonstrated improvement at their first follow-up visit. Our response rate is similar to that of a multicenter randomized controlled trial comparing hydroxychloroquine to acitretin, in which 50% of patients treated with hydroxychloroquine for CLE improved at 8 weeks based on clinical parameters.¹⁰ In the discoid LE population, response to antimalarial agents has been cited to occur in 95% of patients, and response to hydroxychloroquine in 70%,^{11,30} although the lower percentage comes from a study in a nonreferral dermatologic setting. This suggests that our referral population is more resistant to antimalarial drugs than was the nonreferral population.¹⁹

In patients for whom hydroxychloroquine therapy failed, we detected a significant reduction in CLASI activity scores with initiation of hydroxychloroquine-quinacrine, which supports the work of Cavazzana et al,¹³ which demonstrated improvement with hydroxychloroquine-quinacrine therapy by using an unvalidated method of retrospectively assigning CLASI scores. In addition, for nonresponders at the first follow-up visit after initiation of hydroxychloroquine-quinacrine treatment, we found a decrease in CLASI activity scores for almost all patients, despite their not meeting response criteria. For those with further follow-up, a continued decrease in scores was observed (Figure 4B). Also, patients with consistently mild disease while taking hydroxychloroquine demonstrated response with the addition of quinacrine (Figure 4A), suggesting that adding quinacrine could be helpful in patients with mild disease who desire improvement.

Forty-three percent of patients who continued either hydroxychloroquine or hydroxychloroquine-quinacrine demonstrated response with continuation of their respec-

tive antimalarial therapy (n=18). One of 5 initial nonresponders to hydroxychloroquine treatment and 2 of 5 initial nonresponders to hydroxychloroquine-quinacrine therapy were responders with continuation of their respective antimalarial therapy (Figure 2B and Figure 4B). These data support the recommendation of continuing antimalarial therapy beyond 2 months, even if the patients do not initially demonstrate improvement.⁶

Two previous articles have addressed the use of chloroquine-quinacrine combination therapy. Feldmann et al¹⁴ found skin lesions improved significantly or cleared totally in all SCLÉ and one-half of chronic LE cases. Lipsker et al¹⁵ found that three-quarters of DLE, all SCLÉ, and all DLE/SCLÉ cases demonstrated complete or greater than 50% clearance of lesions. Our response rate is not as high as those reported in these studies, which may be a reflection of differences in antimalarial drug use. None of the patients in the 2 earlier studies had been treated with hydroxychloroquine-quinacrine before taking chloroquine-quinacrine, which is in contrast to our patients for whom hydroxychloroquine-quinacrine treatment had failed in the past.

There are several limitations to our study. As a result of both small sample size and a wide range of CLE subtypes, we could not draw any conclusions regarding differences in treatment response based on CLE subtype. Larger studies are necessary to evaluate response to antimalarial agents and any differences across CLE subtypes. Our use of both change and percentage change criteria to determine response²⁸ made apparent that percentage change may not be as meaningful with very low (eg, 0, 1) and high CLASI scores. Studies to evaluate the use of the CLASI across disease severity subtypes would be helpful in determining when change or percentage change is most appropriate to use. In addition, when the criteria for response were determined, high specificity was favored to minimize the misclassification of patients as responders who did not experience a true clinical improvement.²⁸ As such, the sensitivity is lower, increasing the number of patients classified as nonresponders who experienced a true clinical improvement. Finally, in our referral population, we see a wide variety of CLE subtypes¹⁹ and are more likely to see treatment-resistant cases. Although this selection bias limits the generalizability of our results, it allows us to better characterize treatment response in an antimalarial drug-resistant population and to understand which patients will benefit from immunosuppressive, immunomodulator, or investigational drug therapies.

Overall, this prospective study provides evidence supporting the use of hydroxychloroquine-quinacrine for treating patients with CLE who do not respond to hydroxychloroquine. It also demonstrates that continuing hydroxychloroquine or hydroxychloroquine-quinacrine treatment can be beneficial, even in the absence of initial response.

Accepted for Publication: April 22, 2011.

Published Online: July 18, 2011. doi:10.1001/archdermatol.2011.191

Correspondence: Victoria P. Werth, MD, Department of Dermatology, Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, Ste 1-330A, Philadelphia, PA 19104 (werth@mail.med.upenn.edu).

Author Contributions: Ms Chang and Dr Werth had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Chang and Werth. *Acquisition of data:* Chang, Piette, Foering, Okawa, and Werth. *Analysis and interpretation of data:* Chang, Piette, Foering, Tenhave, and Werth. *Drafting of the manuscript:* Chang. *Critical revision of the manuscript for important intellectual content:* Chang, Piette, Foering, Tenhave, Okawa, and Werth. *Statistical analysis:* Chang and Tenhave. *Obtained funding:* Chang and Werth. *Administrative, technical, and material support:* Chang, Piette, Foering, Okawa, and Werth. *Study supervision:* Werth.

Financial Disclosure: None reported.

Funding/Support: This work was supported by National Institutes of Health grant NIH K24-AR 1802207 (Dr Werth) and a grant from the Doris Duke Charitable Foundation to the Perelman School of Medicine at the University of Pennsylvania to fund Clinical Research Fellow Ms Chang.

Additional Contributions: We would like to thank Lynne Taylor, PhD, for her help with statistical analysis.

REFERENCES

1. Payne J. A postgraduate lecture on lupus erythematosus. *Clin J*. 1894;4(5):223-229.
2. Office of the Surgeon General. Circular letter N 153: the drug treatment of malaria, suppressive and clinical. *JAMA*. 1943;123(3):205-208.
3. Page F. Treatment of lupus erythematosus with mepacrine. *Lancet*. 1951;2(6687):755-758.
4. Isaacson D, Elgart M, Turner ML. Anti-malarials in dermatology. *Int J Dermatol*. 1982;21(7):379-395.
5. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options part II. *J Am Acad Dermatol*. 2010;(Aug):23.
6. Wozniacka A, McCauliffe DP. Optimal use of antimalarials in treating cutaneous lupus erythematosus. *Am J Clin Dermatol*. 2005;6(1):1-11.
7. Kalia S, Dutz JP. New concepts in antimalarial use and mode of action in dermatology. *Dermatol Ther*. 2007;20(4):160-174.
8. Wozniacka A, Carter A, McCauliffe DP. Antimalarials in cutaneous lupus erythematosus: mechanisms of therapeutic benefit. *Lupus*. 2002;11(2):71-81.
9. Bezerra EL, Vilar MJ, da Trindade Neto PB, Sato EI. Double-blind, randomized, controlled clinical trial of clofazimine compared with chloroquine in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2005;52(10):3073-3078.
10. Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. *Br J Dermatol*. 1992;127(5):513-518.
11. Dubois EL. Antimalarials in the management of discoid and systemic lupus erythematosus. *Semin Arthritis Rheum*. 1978;8(1):33-51.
12. Wallace DJ. Is there a role for quinacrine (Atabrine) in the new millennium? *Lupus*. 2000;9(2):81-82.
13. Cavazzana I, Sala R, Bazzani C, et al. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. *Lupus*. 2009;18(8):735-739.
14. Feldmann R, Salomon D, Saurat JH. The association of the two antimalarials chloroquine and quinacrine for treatment-resistant chronic and subacute cutaneous lupus erythematosus. *Dermatology*. 1994;189(4):425-427.
15. Lipsker D, Piette JC, Cacoub P, Godeau P, Frances C. Chloroquine-quinacrine association in resistant cutaneous lupus. *Dermatology*. 1995;190(3):257-258.
16. Toubi E, Rosner I, Rozenbaum M, Kessel A, Golan TD. The benefit of combining hydroxychloroquine with quinacrine in the treatment of SLE patients. *Lupus*. 2000;9(2):92-95.
17. Jessop S, Whitelaw DA, Delamere FM. Drugs for discoid lupus erythematosus. *Cochrane Database Syst Rev*. 2009;(4):CD002954.
18. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol*. 2005;125(5):889-894.
19. Moghadam-Kia S, Chitek K, Gaines E, et al. Cross-sectional analysis of a collaborative Web-based database for lupus erythematosus-associated skin lesions: prospective enrollment of 114 patients. *Arch Dermatol*. 2009;145(3):255-260.
20. Sontheimer RD. The lexicon of cutaneous lupus erythematosus--a review and personal perspective on the nomenclature and classification of the cutaneous manifestations of lupus erythematosus. *Lupus*. 1997;6(2):84-95.
21. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25(11):1271-1277.
22. Bonilla-Martinez ZL, Albrecht J, Troxel AB, et al. The cutaneous lupus erythematosus disease area and severity index: a responsive instrument to measure activity and damage in patients with cutaneous lupus erythematosus. *Arch Dermatol*. 2008;144(2):173-180.
23. Erceg A, Bovenschen HJ, van de Kerkhof PC, de Jong EM, Seyger MM. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus. *J Am Acad Dermatol*. 2009;60(4):626-632.
24. Krathen MS, Dunham J, Gaines E, et al. The Cutaneous Lupus Erythematosus Disease Activity and Severity Index: expansion for rheumatology and dermatology. *Arthritis Rheum*. 2008;59(3):338-344.
25. Kreuter A, Gaifullina R, Tigges C, Kirschke J, Altmeyer P, Gambichler T. Lupus erythematosus tumidus: response to antimalarial treatment in 36 patients with emphasis on smoking. *Arch Dermatol*. 2009;145(3):244-248.
26. Kreuter A, Tomi NS, Weiner SM, Huger M, Altmeyer P, Gambichler T. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol*. 2007;156(6):1321-1327.
27. Shah A, Albrecht J, Bonilla-Martinez Z, et al. Lenalidomide for the treatment of resistant discoid lupus erythematosus. *Arch Dermatol*. 2009;145(3):303-306.
28. Klein R, Moghadam-Kia S, LoMonico J, et al. Development of the CLASI as a tool to measure disease severity and responsiveness to therapy in cutaneous lupus erythematosus. *Arch Dermatol*. 2011;147(2):203-208.
29. Savitz DA, Olshan AF. Multiple comparisons and related issues in the interpretation of epidemiologic data. *Am J Epidemiol*. 1995;142(9):904-908.
30. Callen JP. Chronic cutaneous lupus erythematosus: clinical, laboratory, therapeutic, and prognostic examination of 62 patients. *Arch Dermatol*. 1982;118(6):412-416.

PRACTICE GAPS

Optimizing Antimalarial Therapy for Cutaneous Lupus Erythematosus

Antimalarial therapy for cutaneous lupus erythematosus (LE) has existed since the 1950s, and use of these drugs is an on-label therapy for systemic LE. However, in my experience, they are often not used for a long enough time for cutaneous LE before being abandoned for other drugs, which although effective, may

carry more risk and may not have the secondary benefits that antimalarial agents have. We have available in all pharmacies 2 antimalarial preparations, hydroxychloroquine hydrochloride and chloroquine phosphate. Until roughly a decade ago, quinacrine hydrochloride was also available. After its removal from the marketplace, it