Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment

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Background: Reports suggest that cigarette smoking might interfere with the effectiveness of antimalarial therapy as first-line treatment for cutaneous lupus erythematosus. Patients refractory to this treatment often must be treated with potentially more toxic regimens.

Objective: Our purpose was to examine the effects of cigarette smoking on the therapeutic response to antimalarial agents in patients with discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE).

Methods: A total of 61 patients (47 DLE, 14 SCLE) were selected on the basis of the following criteria: (1) skin biopsy was consistent with cutaneous LE, (2) a smoking history was available, and (3) an adequate trial of antimalarial therapy was completed. Patients were classified as antimalarial responders or nonresponders on the basis of descriptions in their medical records. Two-by-two table analysis was performed comparing response rates in smokers versus nonsmokers.

Results: A significant difference ($P<.0002$) in the antimalarial response rate was observed for smokers (40%) versus nonsmokers (90%).

Conclusion: These results indicate that patients with cutaneous LE who smoke are significantly less likely to respond to antimalarial therapy. (J Am Acad Dermatol 2000;42:983-7.)

Clinicians involved in the management of patients with discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) are aware of the challenges that accompany treatment of these patients, particularly those with antimalarial-refractory disease. Since antimalarials first became widely used for LE in the 1950s, they have remained first-line therapeutic agents. These medications are considered effective in the treatment of cutaneous LE, with response rates as high as 75% to 95%.$^{1,2}$ However, there does exist a minority of patients who fail to respond to antimalarial agents, making necessary the use of potentially more toxic regimens. Callen$^3$ and Duna and Cash$^4$ have previously addressed this issue with detailed discussions of managing antimalarial-refractory LE skin disease.

Sontheimer$^5$ first suggested that cigarette smoking might interfere with antimalarial efficacy in treating patients with cutaneous LE. More recently, Rahman, Gladman, and Urowitz$^6$ examined antimalarial-treated cutaneous LE patients and compared lesion clearing rates in smokers versus nonsmokers. They concluded that smoking interferes with the efficacy of antimalarial therapy because only 3 of 17 smokers versus 9 of 17 nonsmokers with cutaneous LE had complete clearing of lesions by 6 months ($P<.035$). The purpose of our study is to further investigate the relationship between smoking and response to antimalarial therapy in patients with DLE and SCLE.

METHODS

A patient list was generated by computer search of all patients seen in either outpatient or inpatient settings at University of North Carolina Hospitals with a diagnosis code for cutaneous LE between 1994 and 1998. All charts were carefully reviewed, and patients were selected for inclusion if the following criteria were met: (1) a skin biopsy was consistent with cutaneous LE, requiring vacuolar change of the basal keratinocytes, (2) a smoking history was...
recorded, and (3) an adequate trial of antimalarial therapy was completed with documentation of the treatment response. An adequate trial of antimalarial therapy was arbitrarily defined as hydroxychloroquine 200 to 400 mg/day for 8 weeks or more or chloroquine 250 mg/day for 5 weeks or more, based on previous recommendations. Regimens that included quinacrine were permitted. Patients were divided into either smokers or nonsmokers at time of therapy.

Response to therapy was determined by reviewing the first follow-up visit recorded after 8 weeks or more of hydroxychloroquine or 5 weeks of chloroquine therapy. Patients were initially divided into 4 outcome categories on the basis of descriptions of their lesions from their medical records: total/near complete clearing of skin lesions, partial clearing (decreased size or number) of skin lesions, no change in skin lesions, or worsening (increased size or number) of skin lesions. For statistical analysis, those experiencing total/near complete and partial clearing were considered responders, whereas those with no change and worsening were considered nonresponders. The analysis consisted of data tables constructed for the DLE patients, the SCLE patients, and the total population using two-by-two tables for retrospective studies with TRUE EPISTAT software (Richardson, Tex). Two-tailed P values are reported.

RESULTS

A total of 274 patients were originally identified by computer search. Of these patients, 213 were excluded for the following reasons: 138 had neither DLE nor SCLE or never received antimalarials, 23 did not have a recorded treatment response, 22 did not have a recorded smoking history, 11 had no biopsy information, 8 records were not available, 7 lacked both a recorded smoking history and a recorded treatment response, 3 could not tolerate antimalarials for an adequate trial period, and one received an antimalarial dose that exceeded the recommended dosage guidelines. Sixty-one patients met all 3 devised criteria for inclusion in this study. These included 47 patients with DLE (32 smokers and 15 nonsmokers) and 14 with SCLE (8 smokers and 6 nonsmokers). There were 5 ex-smokers, all of whom had quit smoking for more than 1 year. They were included with the nonsmokers. Of the 61 patients, 43 were female, and the racial breakdown was as follows: 31 white, 26 black, 2 Hispanic, 1 Asian, and 1 Native American.

Within the DLE group, 17 patients were reported to have generalized disease, whereas the remainder of patients had lesions confined to the head and neck. Subtypes were reported in 10 of 14 SCLE patients. Five patients had annular lesions, 4 had psoriasiform lesions, and 1 patient was reported as having elements of both subtypes.

Hydroxychloroquine was the antimalarial used in 59 of the 61 patients; 47 of these were treated with 400 mg/day, and the remaining 12 received 200 mg/day. Two DLE patients were treated with chloroquine 250 mg/day instead of hydroxychloroquine. Both had previously failed to respond to hydroxychloroquine.

The average duration of antimalarial treatment at the time of response assessment was 10 weeks, with a range of 8 to 13 weeks. In the nonsmoking group there were 19 responders and 2 nonresponders. Of the smokers, there were 16 responders and 24 nonresponders. There was a significant difference (P < .0002) in the response rate to antimalarial therapy for smokers (40%) versus nonsmokers (90%) (Table I). Analysis of DLE patients separately also identified a significant difference (P < .0004) in response rate for smokers (38%) versus nonsmokers (93%) (Table II). As for SCLE patients, 50% of smokers and 83% of nonsmokers responded; however, the difference was not significant (P > .05) (Table III). The response rate based on the number of packs of cigarettes smoked per day was determined (Table IV). Those who smoked the most packs per day had the lowest response rate. Absent from Table IV are 4 patients (3 responders, 1 nonresponder) identified as smokers with no amount of cigarettes recorded in their medical records.

When patients with DLE who were receiving antimalarial therapy along with prednisone or cytotoxic
agents were eliminated from this analysis, the response rates were still significantly different: 37% for smokers versus 89% for nonsmokers ($P < 0.02$). Topical steroids were used more frequently in the antimalarial nonresponder group than in the responder group (38% vs 12%, respectively).

**DISCUSSION**

This study demonstrates that patients with cutaneous LE who smoke, specifically those with discoid lesions, have a significantly lower response rate to antimalarial therapy than those who do not smoke. The same conclusion is suggested by the trend in the SCLE group; however, the numbers of patients with SCLE ($n = 14$) are too small to show a significant difference. These results support the earlier study by Rahman, Gladman, and Urowitz\(^6\) that showed complete clearing of lesions in 18% of smokers and 53% of nonsmokers ($P < 0.035$) for DLE and SCLE patients combined. Interestingly, all of the 14 patients (10 DLE and 4 SCLE) in our study with total or near complete clearing of their skin lesions were nonsmokers, and all 8 (6 DLE, 2 SCLE) whose skin lesions worsened while receiving antimalarial therapy were smokers.

Chloroquine was the predominant antimalarial used in the Rahman, Gladman, and Urowitz study (28/36 patients),\(^6\) whereas in our study, all of the 61 patients had received hydroxychloroquine. Two of our patients were switched to chloroquine after failing to respond to hydroxychloroquine. These 2 patients also failed to respond to chloroquine. Most of our patients were treated with 400 mg/day of hydroxychloroquine; however, 12 (8 DLE, 4 SCLE) of the patients only received 200 mg/day. Three of the 12 patients reported lightheadedness while receiving 400 mg/day. One patient experienced gastrointestinal upset on the higher dose, and 1 presented with a history of pancytopenia while taking 400 mg/day. The remaining 7 patients were treated with only 200 mg for unknown reasons. Nine of these 12 patients, 4 of whom smoked, responded to the lower dose, but it is important to note that all of the patients who had total or near complete clearing of lesions were treated with 400 mg/day. This fact raises the question of whether a better response could have been obtained if all patients had received 400 mg/day.

Statistical analysis of the 39 DLE patients who were treated with the higher dose of hydroxychloroquine still shows a significant difference in response rates of smokers versus nonsmokers ($P < 0.002$). There were 17 nonresponders in this 400 mg/day hydroxychloroquine-treated DLE group. All but 1 were smokers. Twelve of these 17 patients continued hydroxychloroquine therapy for 16 weeks or longer. However, none of these patients experienced clearing of their skin lesions during this extended treatment period. The activity of skin lesions in 2 of these patients waxed and waned over the ensuing months despite maintenance of hydroxychloroquine at 400 mg/day. Skin lesions improved in 2 other patients, including the only nonsmoker in this group, but only after prednisone was added to their regimen. From this analysis, it appears that smokers with DLE who do not show appreciable improvement after 8 to 12 weeks of hydroxychloroquine (400 mg/day) are unlikely to have a dramatic improvement with more prolonged courses of therapy.

Although the focus here is on the fact that the majority of smokers did not respond to therapy, 40% of smokers did improve with antimalarial medications. Although none of the smokers had total or near complete clearing during the first 2 to 3 months, 3 of 12 smokers with DLE (and 2 of 4 nonsmokers with DLE) who showed partial improvement after 2 to 3 months of antimalarial therapy later cleared while being maintained on this therapy.

Previous reports have indicated that the addition of quinacrine may improve the response in patients who have not responded to therapy with hydroxychloroquine or chloroquine alone.\(^3,4,8,9\) Four patients with DLE and one with SCLE (all smokers) who did not respond to hydroxychloroquine alone were later treated with the combination of hydroxychloroquine 400 mg/day and quinacrine 100 to 200 mg/day for a minimum of 1 month. (Note that quinacrine was suggested in other nonresponders,

**Table III.** Response to antimalarials in SCLE patients

<table>
<thead>
<tr>
<th></th>
<th>Total ($n = 14$)</th>
<th>Smokers ($n = 8$)</th>
<th>Nonsmokers ($n = 6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Response rate ($P &gt; 0.05$)</td>
<td>50%</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

**Table IV.** Packs per day (ppd) smoked by responders vs nonresponders

<table>
<thead>
<tr>
<th></th>
<th>1/2 ppd</th>
<th>1 ppd</th>
<th>2 ppd</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of responders</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>No. of nonresponders</td>
<td>5</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Response rate</td>
<td>50%</td>
<td>35%</td>
<td>17%</td>
</tr>
</tbody>
</table>

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\(^{3,4,8,9}\) Jewell and McCauliffe - 985 J Am Acad Dermatol Volume 42, Number 6
but patients had difficulty procuring it.) With the additional antimalarial, one patient showed mild improvement at 1 month, but then was lost to follow-up. One patient reported urticaria with the addition of quinacrine, although no improvement had occurred with 2 months of therapy. The remaining 3 patients reported no change or worsening of skin lesions.

Only 2 of the 26 patients who did not respond to antimalarial therapy were nonsmokers. One of these had systemic LE with discoid lesions on his scalp, face, chest, and upper extremities. The skin lesions did not improve despite 6 months of hydroxychloroquine at 400 mg/day. However, the lesions did improve after the patient’s prednisone dose was increased from 5 to 10 mg every other day to 10 mg every day. The other nonresponder had quit smoking 7 years before initiation of antimalarial therapy. This patient failed to respond to hydroxychloroquine at 200 mg/day but, during the next year, the skin almost completely cleared after 5 months of hydroxychloroquine at 400 mg/day.

Of the 47 DLE patients, 17 had disseminated disease (7 were responders). In the remainder of patients, the lesions were confined to the head and neck. Of the 17 with disseminated disease, 12 were smokers, a proportion similar to that of the entire DLE study population. Within the total DLE and SCLE population, 15 patients also met the criteria for systemic LE. Of these, there were 9 responders (3 smokers) and 6 nonresponders (5 smokers).

Most of the SCLE patients were noted in the medical record as having either psoriasiform or annular subtypes. There was no apparent difference in response among the different subtypes. However, the subtype was not known or not recorded in 3 of the 5 nonresponders.

The majority of the patients in this study were smokers. The numbers of smokers are as follows: 40 of 61 total patients (66%), 32 of 47 DLE patients (68%), and 8 of 14 SCLE patients (57%). However, a 1995 Morbidity and Mortality Weekly Report indicated that only 28% of adults living in North Carolina (the state where this study was conducted) smoke. There are several possible reasons why there were a disproportionate number of smokers in our study. Because this study was conducted at a large academic medical center, a number of cases were referred by outside physicians. It is possible that patients who did not respond initially to antimalarial therapy were selected by referral bias. It may also be that smoking histories in nonsmokers were more frequently omitted from the medical records so a disproportionate number of nonsmokers were excluded from the study. The large percentage of smokers in this study also raises the possibility that smoking may be a risk factor for cutaneous LE. Previous reports have indicated that smoking may be a risk factor for autoimmune disease, including systemic LE and DLE. In fact, a recent review of 28 DLE patients from a private dermatology practice found a prevalence of smoking in DLE patients to be 82% versus 22% in age- and sex-matched controls.

The response rate and the amount of cigarettes reportedly smoked were found to be inversely related (see Table IV). In fact, only 1 of 6 patients who smoked 2 packs per day responded to antimalarial therapy. These results suggest that the effect of cigarette smoking on the efficacy of antimalarial medications may be dose-related.

One patient with DLE attempted to quit smoking during his course of therapy. He was treated with hydroxychloroquine 200 mg twice daily without improvement for 6 months before quitting smoking. Follow-up visits at 1 and 2 months after quitting indicated a decreased number of lesions. However, the patient was seen again 4 months after quitting for an exacerbation of his skin disease when it was noted that he had resumed smoking. It is possible that the improvement was related to his brief cessation of smoking. Sontheimer, in fact, reported that several of his patients with antimalarial-refractory cutaneous LE improved dramatically after cessation of cigarette smoking, without any other changes in therapy.

Previously published studies suggest two possible mechanisms by which smoking interferes with the efficacy of antimalarial medications. It has been proposed that antimalarials exert their effects by stabilizing lysosomal membranes. Both nicotine and antimalarial drugs are lysosomotrophic, meaning that they are sequestered in lysosomes. Nicotine may inhibit the stabilizing effect of antimalarials by blocking their accumulation within lysosomes because nicotine has been shown to strongly inhibit the uptake of chloroquine in cultured cells. Another possibility is that smoking may interfere with the metabolism of antimalarial drugs. Cigarette smoking was found to enhance the elimination of a single dose of quinine sulfate, an antimalarial medication structurally similar to chloroquine and hydroxychloroquine. Although the metabolism of antimalarials is not well understood, it is possible they are inactivated by the cytochrome P-450 enzyme complex. Polycyclic aromatic hydrocarbons found in cigarette smoke are known potent P-450 inducers.

A fault with this and any study that examines the adverse effects of smoking, as is pointed out by Schein in an article reviewing smoking and drug interactions, is the fact that smokers are different from nonsmokers in more ways than the use of ciga-
It has been found that smokers on average consume more caffeine, alcohol, analgesics, laxatives, and hypnotics than do a similar cohort of nonsmokers. It is thus possible that some other factor associated with smoking affects antimalarial efficacy. Our results indicate that smokers with DLE or SCLE are less responsive to antimalarials than are nonsmokers. Although there is no shortage of data on the adverse effects of cigarette smoking, this analysis provides clinicians with yet another reason why cutaneous LE patients should quit smoking. However, attempts to quit smoking, even at a physician’s urging, are often unsuccessful if they are ever even attempted. Therefore alternative therapies for control of cutaneous LE are more likely to be needed by patients who smoke.

In summary, this retrospective analysis provides evidence that smoking inhibits antimalarial responsiveness. Additionally, we find preliminary evidence that this inhibition is dose-related and may be reversible with smoking cessation. Further studies are needed to better define the mechanism by which smoking affects antimalarial efficacy in cutaneous LE. Studies are also needed to determine whether smoking similarly affects the efficacy of antimalarials in treating the systemic manifestations of LE (eg, arthralgia, myalgia, fatigue) and in treating other disorders.

REFERENCES

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