Lupus Erythematosus Tumidus

Response to Antimalarial Treatment in 36 Patients With Emphasis on Smoking

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Objective: To determine the efficacy of antimalarial drug use in patients with lupus erythematosus tumidus.

Design: Retrospective single-center study.

Setting: Dermatologic clinic at a university hospital.

Patients: Thirty-six patients with multifocal lupus erythematosus tumidus.

Intervention: Treatment with either chloroquine phosphate or hydroxychloroquine sulfate.

Main Outcome Measures: Cutaneous Lupus Erythematosus Disease Area and Severity Index score.

Results: Treatment with antimalarial drugs resulted in a significant reduction in the Cutaneous Lupus Erythematosus Disease Area and Severity Index score, from 4 (range, 2-8) at baseline to 1 (range, 0-6) after 3 months of therapy (P < .001). Twenty-two patients (61%) exhibited complete or almost complete clearance of skin lesions, consistent with a clinical score of 0 or 1. No difference in efficacy was noted between the chloroquine-treated group and the hydroxychloroquine-treated group (P = .40).

Adverse effects (nausea, dizziness, and headache) occurred only in patients treated with chloroquine. Twenty-eight patients (78%) were smokers, and smokers had a significantly higher mean (SD) clinical score than non-smokers (5.1 [1.8] vs 3.3 [1.6]; P = .03). Moreover, smokers had a significantly lower reduction in clinical score with antimalarial treatment compared with nonsmokers (r = 0.30; P = .03; 95% confidence interval, −0.05 to 0.57). Eighty-eight percent of nonsmokers (7 of 8 patients) but only 57% of smokers (16 of 28 patients) had a clinical score of 1 or 0 after 3 months of treatment with antimalarial drugs.

Conclusions: These retrospective study findings demonstrate that antimalarial treatment is highly effective in multifocal lupus erythematosus tumidus. Lower incidence of adverse effects and equal efficacy might favor the use of hydroxychloroquine. Patients who smoke should be encouraged to join smoking cessation programs because they will respond better to antimalarial treatment.

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Lupus erythematosus (CLE) is a highly photosensitive skin disorder with distinct clinical and histopathologic characteristics. Most experts nowadays agree that LET is a distinct subtype of cutaneous lupus erythematosus (CLE). LET does not resolve with residual scarring and hyperpigmentation or hypopigmentation. Histopathologic characteristics of LET include perivascular and periaxial lymphocytic infiltrates as well as interstitial mucin deposition. In contrast to DLE or SCLE, LET shows no or only slight vacuolar degeneration of the dermoepidermal junction.

Although no treatment guidelines exist, antimalarial drugs are usually recommended as first-line systemic treatment of CLE. Antimalarial drugs significantly improve skin lesions in approximately 75% to 95% of patients with CLE. Evidence exists that cigarette smoking interferes with the efficacy of antimalarial drugs in CLE. To date, only limited data are available on antimalarial treatment for LET. The larg-
The present article is a retrospective evaluation of antimalarial drugs in patients with multifocal LET using a recently published clinical score for CLE. Moreover, we sought to determine whether differences exist in efficacy between chloroquine phosphate and hydroxychloroquine sulfate and whether smokers with LET are less responsive to antimalarial treatment.

METHODS

PATIENTS

Fifty-one patients with LET were treated at the outpatient unit for connective tissue diseases at the dermatologic clinic at Ruhr University Bochum, Bochum, Germany. The observation period was 2 years (January 1, 2006, through December 31, 2007). To be eligible for this retrospective study, patients were required to meet the clinical and histopathologic criteria for LET published by Kuhn et al. Only patients with multifocal LET, defined as at least 3 lesions of 2 cm or larger in greatest diameter, were included. Exclusion criteria were as follows: pregnancy or lactation, concomitant systemic corticosteroid therapy, any concomitant internal immunomodulating or immunosuppressive therapy, and any concomitant topical therapy (eg, with topical corticosteroids or topical calcineurin inhibitors). Additionally, topical therapy was restricted to the use of emollients and sunscreens. As a standard workup in all patients with CLE, a detailed medical history (including current medications, comorbidities, and smoking status) and physical examination, urinalysis, chest radiography, echocardiography, and ultrasonography of the abdomen were performed in each patient. Serologic analysis included complete blood cell count, antinuclear antibodies, screening for extractable nuclear antibodies (including anti-Ro and anti-La antibodies, anti-Smith antibodies, anti-U1-Ribonucleoprotein antibodies, antihistone antibodies, antitopoisomerase-I antibodies, and anti-Jo-1 antibodies), anti-double-stranded deoxyribonucleic acid antibodies, rheumatoid factor, circulating immune complexes, complement components (C3 and C4), C-reactive protein, immunoglobulin levels (IgA, IgM, and IgG), and routine blood chemistry testing. Appropriate institutional review board approval was obtained for review of patient medical records.

TREATMENT PROTOCOL

Patients treated with hydroxychloroquine received a maximum daily dose of 5 to 6 mg/kg of body weight, resulting in a total dose of 400 mg of hydroxychloroquine sulfate. Patients treated with chloroquine received a maximum daily dose of 3 to 4 mg/kg of body weight, resulting in a total dose of 250 mg of chloroquine phosphate. In contrast to hydroxychloroquine therapy, the regimen in all patients receiving chloroquine phosphate therapy was 500 mg/d for the first 14 days, followed by tapering to 250 mg/d. The decision to treat patients with either chloroquine or hydroxychloroquine was made on the basis of personal preference of the treating physician. Neither extent of disease nor smoking status influenced the choice of drug. In case of gastrointestinal (eg, nausea and vomiting) or neurologic (eg, headache, dizziness, or insomnia) adverse effects, daily dosage of both antimalarial drugs was halved. Blood tests including complete blood cell count, serum chemistry including glucose and electrolyte levels, and urinalysis were performed every 4 weeks during antimalarial treatment for the first 3 months and every 3 months thereafter. Yearly ophthalmologic evaluations were performed in all patients.

CLINICAL EVALUATION

Skin involvement before and after 3 months of therapy with either chloroquine or hydroxychloroquine was assessed using the previously validated Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). In brief, the instrument has separate scores for damage and activity of CLE lesions. The degree of erythema (ranging from absent to dark red/purple on a scale of 0 to 3) and scale/hypertrophy (ranging from absent to verrucous/hypertrophic on a scale of 0 to 2) is assessed in 13 anatomical locations (scalp, ears, nose including malar area, rest of the face, V area of the neck, posterior neck or shoulders, chest, abdomen, back and buttocks, arms, hands, legs, and feet). Moreover, mucous membrane lesions (absent or lesion/ulceration) and alopecia (ranging from absent to focal or widespread in more than 1 quadrant of the scalp) are documented. Adding the subscores yields the total activity score. In this study, only the activity score was used because LET typically does not result in damage including scarring, atrophy, and hyperpigmentation or hypopigmentation. All patients were clinically evaluated by the same investigator (A.K., R.G., C.T., or J.K.) at baseline and after 3 months of treatment.

STATISTICAL ANALYSIS

Data analysis was performed using a commercially available statistical package (MedCalc Software, Mariakerke, Belgium). Distribution of data was assessed using the D'Agostino-Pearson test. Nonnormally distributed data are expressed as median (range). Normally distributed data were assessed using the independent t test. The Wilcoxon test was used for analysis of paired data. Categorical data were assessed using the x² test. The Kendall τ coefficient of correlation (τ) was also calculated. P < .05 was considered statistically significant.

RESULTS

Of the 51 patients with LET treated with antimalarial drugs in the observation period, 15 did not meet the study inclusion criteria (5 patients had only monofocal disease and 10 were receiving concomitant systemic or topical therapy). Thus, 36 patients with multifocal LET were included: 21 women (58%) and 15 men (42%) with a mean range age of 47.4 (24-70) years. Fifty-eight percent of LET lesions were located on the face, 39% on the back, 22% on the chest, and 19% on the arms. None of the 36 patients had signs or symptoms of systemic involvement or had ≥4 criteria or more of the American College of Rheumatology for the diagnosis of systemic lupus erythematosus. Antinuclear antibodies or other immunoserologic findings were not observed except for low complement components (C3 and C4) in 2 patients. Mild leukocytosis was present in 8 patients, all of whom were smokers. Insufficient pretreatment with topical and systemic corticosteroids had been administered in 18 patients (50%) and 6 patients (17%), respectively. Twelve patients (33%) had not received any therapy.
Twenty-six patients were treated with chloroquine, and 10 patients were treated with hydroxychloroquine. Overall, a significant decrease in the CLASI score from a median of 4 (range, 2-8) at baseline to a median of 1 (range, 0-6) after 3 months of therapy was observed ($P < .001$; Figure 1). Twenty-two patients (61%) exhibited complete or almost complete clearing of skin lesions (CLASI score of 0 or 1). There was no difference in efficacy between the 2 antimalarial drugs (chloroquine and hydroxychloroquine; $P = .40$). In most patients, initial signs of improvement were noted after 4 weeks of antimalarial treatment. There was no correlation between duration of disease and response to treatment. Adverse effects (nausea in 5 patients and dizziness and headache in 2 patients) were experienced only by patients treated with chloroquine. Routine laboratory testing during treatment with both antimalarial drugs did not reveal any hematologic or hepatic adverse effects.

Twenty-eight patients (78%) were smokers (approximately 10-20 cigarettes per day), and smokers had a significantly higher mean (SD) CLASI score compared with nonsmokers (5.1 [1.8] vs 3.3 [1.6]; $P = .03$). Smoking significantly correlated with a lower CLASI score reduction with antimalarial treatment compared with nonsmoking ($r = 0.30, P = .03; 95\%$ confidence interval, $-0.051$ to 0.574). When comparing the percentage of patients in whom skin lesions completely or almost completely cleared (CLASI score 1 or 0) after 3 months of treatment with antimalarial drugs, CLASI score was 1 or 0 in 88% of nonsmokers (7 of 8 patients) compared with only 57% of smokers (16 of 28 patients). Representative clinical features are shown in Figure 2 and Figure 3. Extrafacial (eg, back, chest, or arms) and widespread LET (affecting 3 anatomic regions) were observed only in smokers.

One patient refused follow-up. Of the remaining 35 patients, 29 (83%) had complete clearance of skin lesions within a treatment period of at least 6 months. Thirteen patients reported they had quit smoking or had reduced cigarette smoking to a maximum of 5 cigarettes a day. Seven patients with unchanged cigarette consumption (20%) had persistent LET lesions.

**COMMENT**

Findings of this retrospective study demonstrate that antimalarial treatment is highly effective in patients with LET if they do not smoke. Demographic and clini-
cral features in our patients are similar to those in the largest clinical cohort to date, reported by Kuhn et al.5 Lupus erythematosus tumidus predominantly affects the face, is manifested at about the fourth decade of life, and, in contrast to other subtypes of CLE, nearly equally affects men and women. Moreover, systemic involvement is absent in LET, and the occurrence of autoantibodies is rare.

Twenty-eight of our patients (78%) were smokers, which is twice the percentage of smokers (36%) of comparable age (40-49 years) in the general population in Germany.7 Several studies have consistently shown that smoking increases the risk of autoimmune connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus.8-10 Moreover, cigarette smoking seems to be associated with increased disease activity in systemic lupus erythematosus.11 Although the exact pathophysiologic mechanisms of smoking in patients with lupus are still unknown, several plausible hypotheses exist. Cigarette smoke contains tar, nicotine, numerous toxins, and free radicals. Toxins and free radicals can interact with DNA, cause genetic mutations, and induce gene activation responsible for autoimmune diseases.12,13 Smoking increases Fas expression on B- and T-lymphocyte cell surfaces. This leads to increased apoptosis and an increased burden of apoptotic material to be cleared by inefficient clearance mechanisms in patients with autoimmune diseases.14 Moreover, cigarette smoke activates tissue-damaging matrix metalloproteinases and increases cytokines such as interleukin 6, an important marker of inflammation in lupus.15,16 Cigarette smoke condensate is phototoxic and, therefore, is an important trigger for photosensitive disorders such as systemic lupus erythematosus and CLE.17 In agreement with this, several epidermal surface molecules such as intercellular adhesion molecule-1 are increased in smokers, and upregulated expression of this molecule has been demonstrated in primary and UV-induced CLE lesions.16,18

Although, to our knowledge, no data exist on smoking behaviors in patients with LET, a high prevalence of smoking has been reported in patients with other subtypes of CLE.19 Boeckler et al20 retrospectively evaluated 85 patients with CLE and found that 82% were smokers. The largest percentage of smokers had SCLE or lupus panniculitis; however, the number of patients in that study was small. Miot et al21 performed a case-control study in 57 patients with CLE and found that 84% were smokers (48 patients). The percentage of smokers in both studies is similar to our findings in patients with LET: 78% were smokers (28 patients). All patients with DLE with lesions on the arms and all male patients with disseminated DLE were smokers.20,21 In line with this, all of our patients with extrafacial and widespread LET were smokers. Thus, smoking in CLE might be a risk factor for more extensive disease.

Antimalarial drugs are usually used as first-line systemic treatment of CLE. There is evidence that smoking interferes with the efficacy of antimalarial drugs. Rahman et al2 compared 17 smokers and 19 nonsmokers with either DLE or SCLE and found that skin lesions in more than 50% of all nonsmokers but only a minority of smokers completely cleared with antimalarial medication. Jewell and McCauliffe22 evaluated the response to antimalarial drugs in 47 patients with DLE and 14 patients with SCLE. Most were treated with hydroxychloroquine. Those authors found that 90% of all nonsmokers (21 patients) but only 40% of smokers (40 patients) responded to antimalarial drugs. These findings are similar to our results in patients with LET: 88% of nonsmokers vs 57% of smokers. To date, only 1 case report exists on the lower efficacy of antimalarial drugs in LET due to smoking. In that report, hydroxychloroquine significantly improved the skin lesions in a 57-year-old woman after she reduced her cigarette consumption.23 Similarly, all 13 patients who successfully quit or reduced smoking within the observation period of our study had complete clearance of LET skin lesions. The mechanism by which smoking interferes with the efficacy of antimalarial drugs is unknown. Smoking seems to inhibit the effects of antimalarial drugs by blocking their accumulation within lysosomes. Moreover, their elimination seems to be enhanced by induction of the cytochrome P450 enzyme complex.24

Our findings should be viewed in light of the limitations of the study including retrospective design, relatively few patients, and imprecise documentation of patient smoking behavior. For example, serum or urinary cotinine levels would have provided a more accurate estimate of patient smoking status.

In conclusion, this study confirmed that antimalarial drugs are highly effective in LET. Comparing chloroquine and hydroxychloroquine, lower adverse effects and equal efficacy might favor the use of hydroxychloroquine. Patients who smoke should be encouraged to join smoking cessation programs because they will respond better to antimalarial treatment.

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Author Contributions: Dr Kreuter had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kreuter and Gaifullina. Acquisition of data: Gaifullina, Tigges, and Kirschke. Analysis and interpretation of data: Kreuter, Gaifullina, Altmeyer, and Gambichler. Drafting of the manuscript: Kreuter. Critical revision of the manuscript for important intellectual content: Gaifullina, Tigges, Kirschke, Altmeyer, and Gambichler. Statistical analysis: Gambichler. Administrative, technical, and material support: Gaifullina, Tigges, and Kirschke. Study supervision: Kreuter and Altmeyer.

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