Influence of smoking on the efficacy of antimalarials in cutaneous lupus: A meta-analysis of the literature

François Chasset, MD,[a,b] Camille Francès, MD,[b,c] Stéphane Barete, MD, PhD,[b,c] Zahir Amoura, MD, MSc,[a,c] and Laurent Arnaud, MD, PhD[a,c,d]
Paris, France

Background: Interaction between smoking and efficacy of antimalarials, the mainstay of treatment for cutaneous lupus erythematosus (CLE), remains controversial.

Objectives: We systematically reviewed the evidence for such an interaction and performed a meta-analysis to compare the efficacy of antimalarials among smoker versus nonsmoker patients with CLE.

Methods: Observational studies published up to March 2014 in the MEDLINE, Embase, and Cochrane databases were selected if they reported on the efficacy of antimalarials for treatment of CLE, according to smoking status. The strength of association between smoking and cutaneous response rate was expressed using the odds ratio. Individual study odds ratios were combined in the meta-analysis using a random effects model.

Results: Of 240 citations retrieved, 10 studies met inclusion criteria, for a total of 1398 patients. The pooled odds ratio for the response to antimalarials in smoker patients with CLE (n = 797) was 0.53 (95% confidence interval 0.29-0.98) compared with nonsmokers (n = 601).

Limitations: Subgroup analyses for the response to antimalarials considering CLE subtypes, type, and dosage of antimalarials could not be performed because of the lack of available data.

Conclusions: Smoking is associated with a 2-fold decrease in the proportion of patients with CLE achieving cutaneous improvement with antimalarials. Smoking cessation should be considered in patients with CLE and refractory cutaneous involvement. (J Am Acad Dermatol 2015;72:634-9.)

Key words: antimalarials; cutaneous; hydroxychloroquine; lupus erythematosus; smoking; tobacco.

Hydroxychloroquine (HCQ) and chloroquine (CQ) are the mainstay of treatment for cutaneous lupus erythematosus (CLE). However, up to 30% of patients with CLE are not responsive to these treatments.[1]

Factors known to influence the efficacy of antimalarial drugs include patients' exposure to the active drug, with median blood HCQ concentrations

Abbreviations used:

CI:	confidence interval
CLASI:	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE:	cutaneous lupus erythematosus
CQ:	chloroquine
HCQ:	hydroxychloroquine
OR:	odds ratio

From AP-HP, Groupement Hospitalier Pitié-Salpêtrière, E3M Institute, Internal Medicine Department, French National Reference Center for Systemic Lupus Erythematosus[a]; Department of Dermatology and Allergology Tenon Hospital-APHP[b]; Sorbonne Universités, UPMC Univ Paris 06[c]; and INSERM UMR-S 1136, GRC 08, Institut Pierre Louis d'Epidémiologie et Santé Publique.[d]
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Reprint requests: Laurent Arnaud, MD, PhD, AP-HP, Groupement Hospitalier Pitié-Salpêtrière, E3M Institute, Internal Medicine Department, French National Reference Center for Systemic Lupus Erythematosus, 47-83 Bd de l'Hôpital, 75013 Paris, France. E-mail: Laurent.arnaud@psl.aphp.fr.
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found significantly higher in those with complete remission compared with those with treatment failure in CLE.[2] Moreover, the extent of lesions in localized CLE was found more likely to respond to antimalarial drugs compared with disseminated CLE or systemic lupus erythematosus in an observational study.[3]

In addition, cigarette smoking has been inconsistently reported to interfere with antimalarial efficacy.[4] However, the true impact of tobacco on CLE response to HCQ therapy remains controversial, because of conflicting results of previous observational studies and the lack of randomized controlled trials.

Here, we conducted a systematic review of the literature and a meta-analysis to compare the efficacy of antimalarial drugs between smoker and nonsmoker patients with CLE.

CAPSULE SUMMARY

- Impact of smoking on efficacy of antimalarials in cutaneous lupus erythematosus remains controversial.
- Smoking is associated with a 2-fold decrease in the proportion of patients with cutaneous lupus erythematosus achieving cutaneous response with antimalarials.
- Smoking cessation may enhance cutaneous improvement in cutaneous lupus erythematosus, as a result of both direct effects and impact on antimalarials.

METHODS

This meta-analysis was performed in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group.[5] The detailed method and search strategy may be obtained through the corresponding author. Institutional review board approval was not necessary in France for a meta-analysis.

Sources

Two main investigators searched EMBASE, MEDLINE, and the Cochrane Database of Systematic Reviews for original articles without language restrictions.

Study selection

Observational studies were considered if: (1) they included patients with CLE; (2) CLE was defined clinically and confirmed histologically; (3) the number of patients treated with antimalarials was noted; and (4) a 2 × 2 table could be constructed based on the response of CLE to antimalarials, with respect to the smoking status. When the data of interest could not be found in the articles, we contacted the main authors. We excluded the studies for which these data were not available. The quality of studies was assessed using the Newcastle-Ottawa Assessment Scale.[6]

Definitions of smoking and of response to antimalarials

Smoking was defined as tobacco exposure according to the definition used in each study, ie, active smoking at study entry in all but 2 studies[7,8] in which smokers were defined as ever smokers (ie, those who had smoked at any moment in life and may not have been smoking at study entry).

Cutaneous response to antimalarials was defined accordingly to the definition used in each study, ie, by the CLE Disease Area and Severity Index (CLASI)[9] or according to study-specific criteria considering the size and number of lesions.

Statistical analyses

The meta-analysis was performed with software (RevMan, Version 5.0, Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Literature search and characteristics of included studies

Our literature search identified 240 citations of interest, of which 4 prospective[2,8,10,11] and 6 retrospective[3,7,12-15] cohort studies met the inclusion criteria (Fig 1). Visual examination of the funnel plot (Fig 2) revealed no asymmetry and was therefore not suggestive of any publication bias. The publication period of the 10 included studies runs from 1998 to 2014. Sample size varied from 11 to 1002 patients with CLE, with data available for a total of 1398 patients with CLE, including 832 smokers and 566 nonsmokers. The mean age at study entry was 43.4 years (range 38.4-48.5 years) and 76.6% of patients (range 58%-91%) were female. The detailed characteristics of these 10 studies are reported in Table I.

Treatments with HCQ and CQ were prescribed in 1158 and 261 patients, respectively (some patients received more than 1 line of treatment with HCQ or CQ). Cutaneous response to antimalarial drugs was assessed by the CLASI in 5 studies[8,10,12,13] and according to study-specific criteria in 5 studies.[3,7,11,14,15] When the CLASI was used, cutaneous response was defined by either a 4-point or a 20% decrease in the activity score in 4 studies,[7,8,10,12] according to a previously validated definition of improvement,[9] or by a CLASI score of