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Efficacy of antimalarial agents to prevent the progression of discoid lupus erythematosus to systemic lupus erythematosus: A retrospective cross-sectional study

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Abstract

Background: Discoid Lupus Erythematosus (DLE) patients have the potential to developing Systemic Lupus Erythematosus (SLE) at a later time. The prescription of antimalarial agents might be beneficial to prevent this progression but the validated data is still lacking.

Objectives: Our study aimed to explore whether antimalarial agent could slow progression to SLE in DLE patients, adjusting for other potential confounders.

Methods: We retrospectively studied 65 patients who were diagnosed as DLE and attended the outpatient clinic at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between January 1, 2017 and December 31, 2020. We reviewed medical records including history of DLE, SLE signs and symptoms, laboratory findings and treatment options.

Results: Over a total of 458.73 person years (PY), 19 patients (29.23%) eventually progressed to SLE within approximately 1 year. Of these, 15 patients had widespread lesions whereas only 4 patients presented with localized form. The prescription of antimalarial drug was associated with delayed SLE progression in our cohort. Other parameters such as generalized form (IRR 6.243 (95% CI 1.450–26.872); P = 0.014), joint involvement (IRR 5.005 (95% CI 1.931–12.969); P = 0.001) and LE specific skin lesions (IRR 3.799 (95% CI 1.220–11.825); P = 0.021) were considered as strong risk factors in SLE development.

Conclusions: Our study suggested that an antimalarial drug could postpone the SLE development in DLE patients.

Key words: Discoid lupus erythematosus, Systemic lupus erythematosus, Hydroxychloroquine, Chloroquine, Antimalarial drug, Disease progression

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Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with diverse clinical manifestations. The skin is the second most frequent target organ of SLE, known as cutaneous lupus erythematosus (CLE). CLE can be divided into three subtypes: acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE). Discoid Lupus Erythematosus (DLE) is the most common type of CCLE, characterized by a well-demarcated annular erythematous patch or plaque,

located on a photo distribution area. Up to 80% of lesions are usually confined to the head and neck area, known as a localized form, whereas 20% of lesions extend below the neck area, defined as a generalized form.[1]

DLE patients have an increased susceptibility to developing SLE at a later time: the proportion of patients who progress to SLE ranges from 0% to 28%.[2] For this reason, early detection and prevention of SLE progression are of utmost clinical importance. The possible effect of antimalarial agents, especially hydroxychloroquine (HCQ), in slowing the SLE progression among high risk patients has been previously addressed.[3] Despite this, it remains uncertain whether the prescription of antimalarial agents is beneficial in this regard or not. Therefore, we conducted this study with the aim of evaluating the relative effect of antimalarial agent on progression from DLE to SLE.

Methods

This retrospective cross-sectional study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand (COA no.595/2021). All 137 patients diagnosed with DLE and attended the outpatient clinic at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between January 1, 2017 and December 31, 2020 were eligible for the study. DLE diagnosis was based on clinical characteristics and histopathologic findings. Of these, 49 patients were diagnosed as SLE at their first visit and were excluded, as were 3 patients with other connective tissue diseases and 20 patients who became lost to follow-up before January 1, 2021. We obtained the medical records including gender, age, comorbidities, smoking status, duration of DLE, lesion site, the presentation of other cutaneous lupus erythematosus forms (i.e., ACLE, SCLE, CCLE), the presentation of other clinical manifestations related to SLE (e.g., cutaneous vascular disease, alopecia areata, urticaria), date of transition to SLE. Baseline laboratory findings including complete blood count (CBC), urinalysis (UA) were also collected, and antinuclear antibody (ANA) results were retrieved if available. Two cut-point values of serum ANA were identified at 1:80 and 1:1280, dividing the patients into three groups. Information regarding treatment options was also collected from the first visit to December 31, 2020. 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for Systemic Lupus Erythematosus was used for SLE diagnosis.[4]

Analysis time began when DLE symptoms developed; patients who did not develop SLE were censored at the most recent clinic visit when they were known to be free of SLE. Univariable and multivariable Poisson regression was used to calculate incidence rate ratios (IRR) and 95% CI for progression to SLE. Our initial multivariable model included all variables significant at $P < 0.1$ in univariable analysis. The final model with reduced number of predictors was obtained using backwards stepwise elimination to select the multivariable model which minimized Akaike's Information Criteria (AIC). Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using Stata version 15.1 (StataCorp).

Results

Sixty-five patients diagnosed as DLE were enrolled. The median (IQR) age of onset was 53 (38–63) years. The female/male ratio was approximately 5:1. Most of the patients were identified as non-smoker (n = 57, 87.69%) and had comorbidities (n = 37, 56.92%); the most common comorbid conditions were hypertension and dyslipidemia. The median (IQR) duration of DLE was 8.77 (2.75–13.14) years and the lesions were mainly involved on the scalp (n = 41, 63.08%) followed by the face (n = 40, 61.54%) and the ear (n = 25, 40%), respectively. Over a total of 458.73 person years (PY), 19 patients developed SLE within approximately 1 year of DLE onset. Of the 19 patients who developed SLE, 15 patients had widespread lesions whereas only 4 patients presented with localized disease. LE-nonspecific skin lesions such as vasculitis, livedo reticularis or Raynaud's phenomenon commonly occurred in DLE with SLE patients (found in 47.37%), followed by joint involvement (42.11%) and oral ulcer (36.84%). The most common coexisting CLE in DLE with SLE patients was acute form (42.11%). All SLE progression patients in our study had a history of antinuclear antibodies (ANA) positive.

Forty of 65 patients were initiated on antimalarial agent after developing DLE symptoms. HCQ and CQ were prescribed to 38 (58.46%) and 4 (6.15%) patients respectively; two patients received CQ before switching to HCQ. Five of these patients developed SLE with a median (IQR) of 1.75 (0.25–2.5) years after antimalarial drug initiation, whereas the median (IQR) time from antimalarial use to censoring in the 35 patients who did not develop SLE was 4.9 (1.2–11.2) years (**Figure 1**). Regarding the safety profile, 4 out of 38 patients (10.53%) who received HCQ experienced macular toxicity and discontinued the drug, while this event occurred in 1 CQ-treated patient (25%).

In univariate analysis, antimalarial agent administration significantly lowered the risk of SLE progression (IRR 0.681 (95% CI 0.502–0.934); $P = 0.023$). In the final multivariable model, three parameters were independently associated with an increased risk of SLE progression. These were generalized form (IRR 6.243 (95% CI 1.450–26.872); $P = 0.014$), joint involvement (IRR 5.005 (95% CI 1.931–12.969); $P = 0.001$) and LE specific skin lesions (IRR 3.799 (95% CI 1.220–11.825); $P = 0.021$) (**Figure 2**). In this final model, years of antimalarial use remained associated with a decreased risk of progression to SLE (IRR 0.647 (95% CI 0.471–0.887); $P = 0.007$) (**Table 1**).

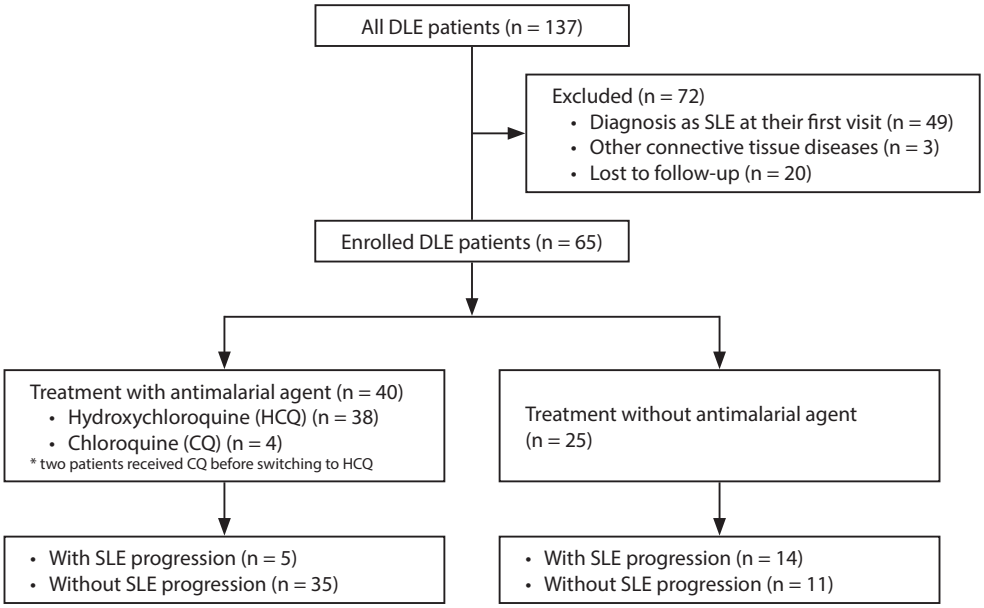

Figure 1. Flow chart of patient enrollment.

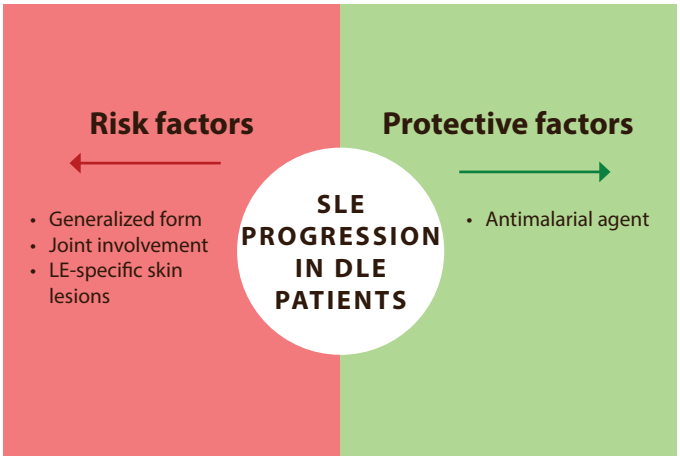

Figure 2. Summary of the risk and protective factors for SLE progression in DLE patients.

Table 1. Univariable/multivariable Poisson regression models. The multivariable model was developed by a backwards selection, successively dropping the variable which would minimize the AIC, until the minimum AIC was reached (N = 65).

Outcome predictor	Univariate			Multivariate		
	IRR	95% Confidential Interval	*P*-value	aIRR	95% Confidential Interval	*P*-value
Female	4.241	0.566–31.771	0.160			
Age	0.972	0.943–1.001	0.067			
Immunological Comorbidities	6.691	1.546–28.961	0.011*			
Generalized DLE	10.448	3.468–31.481	< 0.001*	6.243	1.450–26.872	0.014*
Oral ulcer	3.576	1.408–9.084	0.007*			
Joint involvement	8.036	3.233–19.979	< 0.001*	5.005	1.931–12.969	0.001*
Non-scarring alopecia	0.786	0.299–2.069	0.626			
LE-nonspecific skin lesions	2.639	1.073–6.496	0.035*			
LE-specific skin lesions	8.085	3.285–19.898	< 0.001*	3.799	1.220–11.825	0.021*

Table 1. (Continued)

Outcome predictor	Univariate			Multivariate		
	IRR	95% Confidential Interval	*P*-value	aIRR	95% Confidential Interval	*P*-value
Proteinuria	18.584	7.064–48.894	< 0.001*	3.136	0.963–10.212	0.058
Leukopenia	11.166	4.537–27.480	< 0.001*			
Thrombocytopenia	6.044	1.396–26.158	0.016*			
ANA						
Negative	1 (reference)					
80-640	1.660	0.446–6.181	0.450			
≥ 1280	9.166	3.133–26.815	< 0.001*			
Anti-malarial drug	0.681	0.502–0.934	0.023*	0.647	0.471–0.887	0.007*

*IRR = Incidence rate ratio; aIRR = adjusted incidence rate ratio.

Discussion

The results herein identified the SLE conversion rate, which was similar to previous studies.[2,5] Our progression time was quite rapid when compared to aforementioned data.[5] Furthermore, we confirmed the known hypothesis that generalized lesions, joint involvement and LE specific skin lesions were strong risk factors of being later diagnosed with SLE.[2,6] Thus, a close monitoring and frequent reevaluation were warranted among DLE patients with these specific features.

Regarding our primary outcome, antimalarial agent use was significantly related to SLE progression. The multivariable model suggested that antimalarial agent could significantly reduce the progression to SLE by approximately 35% per year. In line with previous report, HCQ could delay the time from first clinical symptom presentation, to the time when all SLE diagnostic criteria are fulfilled.[3] Moreover, there were some bodies of research which indicated the benefits of this agent in decreasing SLE activity.[7] The mechanism behind these results might be postulated from inhibiting Toll-like receptor activation which consequently reduces interferon-α (IFN-α) synthesis, a key role in SLE pathogenesis.[8] In terms of safety profile, the incidence of macular toxicity was quite low, especially HCQ. As a result, antimalarial agent could offer protection against the development of SLE and may be considered in all DLE patients, not only in generalized patients. However, the strength of our study was limited by the small sample size and the heterogeneous nature of the patients in the population. Also, the details regarding the optimal dose and duration were still required further investigation. Future study with larger population should be conducted to reinforce this protective effect of antimalarial agent.

In conclusion, antimalarial agent could prevent SLE progression in DLE patients. Taken into consideration, the early prescription of this drug might be beneficial and may have a role in all DLE patients, especially who were at high risk for SLE development. More prospective studies are needed to affirm our conclusion.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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