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Title: Long-term efficacy and safety outcomes of lenalidomide for cutaneous lupus erythematosus: a multicenter retrospective observational study of 40 patients

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To the Editor:

Small case series suggested that lenalidomide may be a promising therapeutic option for severe cutaneous lupus erythematosus (CLE).[1–3] The aims of this study were to report the long-term efficacy and safety profile of lenalidomide in CLE patients with focus on patients with associated systemic lupus erythematosus (SLE) and potential factors associated with complete response (CR).

This multicenter retrospective observational case-series enrolled patients with CLE who received lenalidomide after failure of hydroxychloroquine and at least one second-line systemic treatment.

Clinical efficacy was assessed with the cutaneous lupus erythematosus disease and severity index activity[4] (CLASI-A) score at baseline, at first evaluation scheduled after 1 or 3 months, and every 6 months. Cutaneous response was defined as follows: minimal response was defined by a 4-point or 20% decrease in CLASI-A score, partial response (PR) by an improvement of at least 50% and CR by CLASI-A score = 0. Occurrence of relapse, doses at which they occurred and SLE flares were recorded.

A total of 40 patients with CLE (65% had associated SLE) were included (**Table 1**). The median follow-up was 40 months (range: 6-101). Thirty-five patients (88%) previously received thalidomide and stopped because of inefficacy (49%) or poor tolerance (51%). The starting dose of lenalidomide was 5 mg/day in 37 cases. In all, 98% patients had at least a 4-point or 20% decrease in CLASI-A score. The PR rate was 88% after a median treatment duration of 3 months (range: 1-20); 17/35 (43%) patients achieved CR. The PR rate was similar between patients with mild (10/12, 83%), moderate (19/21, 90%) and severe (6/7, 85%) disease activity. However, CR was significantly more frequent in patients with mild and moderate compared with severe activity (17/33, 51% versus 0/7, 0% p=0.01). Among 39 patients with any response,

21 (54%) showed relapse or worsening of CLE, including 13 after a dose reduction. A sustained dose reduction was possible in 22 (55%) patients, with a median minimum effective dose of 2.5 mg/day (range: 0.7-10). Three (8%) patients were able to discontinue lenalidomide because of CR without relapse. The CR rate was significantly decreased in active smokers (HR: 3.17 [95%CI: 1.04-9.67]; p=0.04, log-rank test) as compared with former and never smokers.

During a total of 93 patient-years of follow-up, grade III or IV adverse events were observed in 5 patients (3 arterial thrombosis) (**Table 2**), with 4 (10%) requiring permanent discontinuation of treatment. Therefore, as for thalidomide, the prescription of lenalidomide should be carefully discussed in patients with cardiovascular risk-factors or antiphospholipid syndrome.[5] No onset or worsening of thalidomide-induced neuropathy (n=7) were observed. SLE with articular involvement developed in 1 patient with isolated CLE but no renal flare as previously reported.[3] Eight (31%) of the 26 SLE patients experienced flares and high Safety of Estrogens in Systemic Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score at baseline was significantly higher for SLE patients with than without flares (p=0.005) suggesting that lenalidomide has little or no effect on global SLE activity. This study provides long-term efficacy and follow-up data and confirms the benefit of lenalidomide in refractory CLE.

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Table 1. Characteristics of cutaneous lupus erythematosus (CLE) patients at lenalidomide initiation (n=40)

Demographic data of patients, *n* (%)	
Female sex	35 (88)
Age (years), median (range)	43 (22-71)
Active smoking status, *n* (%)	25 (63)
Body mass index (kg/m²), median (range)	21 (17-37)
Fitzpatrick phototype V and VI, *n* (%)	7 (18)
CLE subtypes, *n* (%)	
Discoid	25 (63)
Discoid and subacute	8 (20)
Discoid and tumidus	4 (10)
Subacute	2 (5)
Discoid and lupus panniculitis	1 (2.5)
Characteristics of SLE patients among total	
SLE, *n* (%)	26 (65)
SELENA-SLEDAI at baseline, median (range)	4 (2-10)
Antiphospholipid syndrome, *n* (%)	3 (7.5)
CLASI-A features	
CLASI-A score at initiation of lenalidomide, median (range)	12 (3-41)
Mild CLE (CLASI-A 0-9), *n* (%)	12 (30)
Moderate CLE (CLASI-A 10-20), *n* (%)	21 (53)
Severe CLE (CLASI-A 21-70), *n* (%)	7 (17)
Previous systemic treatments	
Previous lines of systemic treatment, median (range)	4 (1-9)
Patients who previously received thalidomide, *n* (%)	35 (88)
Thalidomide treatment duration (months), median (range)	10 (0.7-147)
Thalidomide treatment dose (mg), median (range)	100 (25-100)
Treatments associated with lenalidomide, *n* (%)	
Hydroxychloroquine	35 (88)
Low-dose aspirin°	35 (88)
Oral glucocorticoids	13 (30)
Immunosuppressant agents[#]	8 (20)
Topical calcineurin inhibitor	14 (35)

° low dose aspirin was added to prevent thromboembolic risk; # including methotrexate (n=2), mycophenolate mofetil (n=3), azathioprin (n=2), low-dose interleukin 2 (n=1); CLE = cutaneous lupus erythematosus; SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index activity[4]

Table 2. Adverse events and systemic lupus erythematosus (SLE) flares during lenalidomide treatment

Adverse events	***n* (%)**
Grade III or IV adverse event leading to temporary or permanent discontinuation	5 (12.5)
- Cardiovascular event[a]	3 (8)
- Cancer[b]	2 (5)
Other adverse events	
- Neutropenia (grade I-II)	3 (8)
- Asthenia (grade I-II)	9 (23)
Onset of neuropathy or worsening of thalidomide-induced neuropathy (n=7)	0
Data regarding systemic flares	***n* (%)**
Patients with SLE flare[c] (among 26 with SLE)	8 (31)
Severe SLE flare[c]	4 (15)
SLE flare leading to lenalidomide discontinuation (among all patients)	1 (2.5)
Development of SLE among patients with isolated CLE (n = 14)	1 (7)

Data are *n* (%) patients [a] arterial thrombosis (n=1), transient ischemic attack (n=1), acute coronary syndrome (n=1). One patient had antiphospholipid syndrome and one had severe cardiovascular risk factors. Arterial events did not occur in the context of malignancy; [b] ductal breast carcinoma in situ (n=1), gastric cancer (n=1); [c] according to the SELENA-SLEDAI Flare Index