



HAL
open science

Article type: Research letter

Raphael Aitmehdi, Laurent Arnaud, Camille Francès, Patricia Senet, Jean-Benoît Monfort, Tullia de Risi-Pugliese, Annick Barbaud, Fleur Cohen-Aubart, Julien Haroche, Micheline Pha, et al.

► To cite this version:

Raphael Aitmehdi, Laurent Arnaud, Camille Francès, Patricia Senet, Jean-Benoît Monfort, et al.. Article type: Research letter. Journal of The American Academy of Dermatology, 2021, 84 (4), pp.1171-1174. 10.1016/j.jaad.2020.11.014 . hal-03474634

HAL Id: hal-03474634

<https://hal.sorbonne-universite.fr/hal-03474634v1>

Submitted on 10 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 **Article type:** Research letter

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

4
5 Raphael Aitmehdi, MD¹, Laurent Arnaud, MD, PhD², Camille Francès, MD¹, Patricia Senet,
6 MD¹, Jean-Benoît Monfort, MD¹, Tullia de Risi-Pugliese, MD¹, Annick Barbaud, MD, PhD¹,
7 Fleur Cohen-Aubart, MD, PhD³, Julien Haroche, MD, PhD³, Micheline Pha, MD³, Miguel Hie,
8 MD³, Véronique Le Guern, MD⁴, Nathalie Costedoat-Chalumeau, MD, PhD⁴, Arsène
9 Mékinian, MD, PhD⁵, Olivier Fain, MD, PhD⁵, Alexis Mathian, MD, PhD³, Zahir Amoura,
10 MD, MSc³, François Chasset, MD, PhD¹

11
12 ¹Sorbonne Université, Faculté de Médecine, AP-HP, Service de Dermatologie et Allergologie,
13 Hôpital Tenon, F-75020 Paris, France

14
15 ²Service de Rhumatologie, Hôpitaux Universitaires de Strasbourg, Centre National de
16 Références des Maladies Systémiques et Autoimmunes Rares Est Sud-Ouest (RESO),
17 Université de Strasbourg, F-67000 Strasbourg, France

18
19 ³Sorbonne Université, Faculté de Médecine, AP-HP, Groupement Hospitalier Pitié-Salpêtrière,
20 French National Referral Center for Systemic Lupus Erythematosus, Antiphospholipid
21 Antibody Syndrome and Other Autoimmune Disorders, Service de Médecine Interne 2, Institut
22 E3M, Inserm UMRS, Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Paris,
23 France

24

25 ⁴Assistance Publique-Hôpitaux de Paris (AP-HP), Internal Medicine Department, Cochin
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

26 Hospital, Referral center for rare autoimmune and systemic diseases, Paris, France; Université
27 de Paris, Paris, France; INSERM U 1153, Center for Epidemiology and Statistics Sorbonne
28 Paris Cité, Paris, France

30 ⁵Faculté de Médecine Sorbonne Université, AP-HP, Service de Médecine Interne, Hôpital
31 Saint-Antoine, F-75012 Paris, France

33 **Corresponding author:**

34 François Chasset, MD, PhD

35 AP-HP, Service de Dermatologie et d'Allergologie, Sorbonne Université, Hôpital Tenon

36 4 Rue de la Chine 75970 Paris CEDEX 20, France

37 Email: francois.chasset@aphp.fr

39 **Funding sources:** None

41 **Conflict of interest:** None declared

43 **IRB approval status:** not necessary

44 **Statement of any prior presentation:** none

46 **Text word count:** 498 words, **References:** 5, **Tables:** 2

47 **Key words:** lenalidomide; cutaneous lupus erythematosus; systemic lupus erythematosus;
48 long-term efficacy; treatment

49 To the Editor:

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

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

58 Clinical efficacy was assessed with the cutaneous lupus erythematosus disease and severity
59 index activity⁴ (CLASI-A) score at baseline, at first evaluation scheduled after 1 or 3 months,
60 and every 6 months. Cutaneous response was defined as follows: minimal response was defined
61 by a 4-point or 20% decrease in CLASI-A score, partial response (PR) by an improvement of
62 at least 50% and CR by CLASI-A score = 0. Occurrence of relapse, doses at which they
63 occurred and SLE flares were recorded.

64 A total of 40 patients with CLE (65% had associated SLE) were included (**Table 1**). The median
65 follow-up was 40 months (range: 6-101). Thirty-five patients (88%) previously received
66 thalidomide and stopped because of inefficacy (49%) or poor tolerance (51%). The starting
67 dose of lenalidomide was 5 mg/day in 37 cases. In all, 98% patients had at least a 4-point or
68 20% decrease in CLASI-A score. The PR rate was 88% after a median treatment duration of 3
69 months (range: 1-20); 17/35 (43%) patients achieved CR. **The PR rate was similar between**
70 **patients with mild (10/12, 83%), moderate (19/21, 90%) and severe (6/7, 85%) disease activity.**
71 **However, CR was significantly more frequent in patients with mild and moderate compared**
72 **with severe activity (17/33, 51% versus 0/7, 0% p=0.01). Among 39 patients with any response,**

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

73 21 (54%) showed relapse or worsening of CLE, including 13 after a dose reduction. A sustained
74 dose reduction was possible in 22 (55%) patients, with a median minimum effective dose of 2.5
75 mg/day (range: 0.7-10). Three (8%) patients were able to discontinue lenalidomide because of
76 CR without relapse. The CR rate was significantly decreased in active smokers (HR: 3.17
77 [95%CI: 1.04-9.67]; p=0.04, log-rank test) as compared with former and never smokers.

78 During a total of 93 patient-years of follow-up, grade III or IV adverse events were observed in
79 5 patients (3 arterial thrombosis) (**Table 2**), with 4 (10%) requiring permanent discontinuation
80 of treatment. Therefore, as for thalidomide, the prescription of lenalidomide should be carefully
81 discussed in patients with cardiovascular risk-factors or antiphospholipid syndrome.⁵ No onset
82 or worsening of thalidomide-induced neuropathy (n=7) were observed. SLE with articular
83 involvement developed in 1 patient with isolated CLE but no renal flare as previously reported.³
84 Eight (31%) of the 26 SLE patients experienced flares and high Safety of Estrogens in Systemic
85 Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity
86 Index (SELENA-SLEDAI) score at baseline was significantly higher for SLE patients with
87 than without flares (p=0.005) suggesting that lenalidomide has little or no effect on global SLE
88 activity. This study provides long-term efficacy and follow-up data and confirms the benefit of
89 lenalidomide in refractory CLE.

90 **References**

- 1
2
3 91
4 92 1. Cortés-Hernández J, Ávila G, Vilardell-Tarrés M, Ordi-Ros J. Efficacy and safety of
5 93 lenalidomide for refractory cutaneous lupus erythematosus. *Arthritis Res Ther.*
6 94 2012;14(6):R265. doi:10.1186/ar4111
7
8
9 95 2. Fennira F, Chasset F, Soubrier M, Cordel N, Petit A, Francès C. Lenalidomide for
10 96 refractory chronic and subacute cutaneous lupus erythematosus: 16 patients. *Journal of*
11 97 *the American Academy of Dermatology.* 2016;74(6):1248-1251.
12 98 doi:10.1016/j.jaad.2016.01.054
13
14
15 99 3. Braunstein I, Goodman NG, Rosenbach M, et al. Lenalidomide therapy in treatment-
16 100 refractory cutaneous lupus erythematosus: Histologic and circulating leukocyte profile
17 101 and potential risk of a systemic lupus flare. *Journal of the American Academy of*
18 102 *Dermatology.* 2012;66(4):571-582. doi:10.1016/j.jaad.2011.01.015
19
20
21 103 4. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus
22 104 Disease Area and Severity Index): An Outcome Instrument for Cutaneous Lupus
23 105 Erythematosus. *Journal of Investigative Dermatology.* 2005;125(5):889-894.
24 106 doi:10.1111/j.0022-202X.2005.23889.x
25
26
27 107 5. Cesbron E, Bessis D, Jachiet M, et al. Risk of thromboembolic events in patients treated
28 108 with thalidomide for cutaneous lupus erythematosus: A multicenter retrospective study.
29 109 *Journal of the American Academy of Dermatology.* 2018;79(1):162-165.
30 110 doi:10.1016/j.jaad.2018.02.049
31
32
33 111
34
35 112
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

113 **Table 1.** Characteristics of cutaneous lupus erythematosus (CLE) patients at lenalidomide
 114 initiation (n=40)
 115

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 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/m ²), 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 | |

116

117 **Table 2.** Adverse events and systemic lupus erythematosus (SLE) flares during lenalidomide
 1 118 treatment
 2 119

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Adverse events | <i>n</i> (%) |
| 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 | <i>n</i> (%) |
| 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 <i>n</i> (%) 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 | |

30 120

31 121

32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65