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1 **Belimumab for refractory manifestations of cutaneous lupus: a multicenter,**
2 **retrospective observational study of 16 patients**

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43 Belimumab is a fully humanized monoclonal antibody against B-lymphocyte stimulator
44 (BLyS) approved for systemic lupus erythematosus (SLE). A post-hoc analysis of the two
45 pivotal phase III studies showed that belimumab led to a better improvement than placebo on
46 mucocutaneous domains. However, these studies used global scores that do not accurately
47 assess improvement of cutaneous lupus erythematosus (CLE)¹. There is very few data on the
48 efficacy of belimumab using appropriate tools to assess CLE activity, particularly for chronic
49 subtypes^{2,3}. This multicenter, retrospective observational study enrolled histologically
50 confirmed CLE patients, who received belimumab between 2014 and May 2019. Patients
51 were refractory to hydroxychloroquine and received at least two ineffective second-line
52 systemic treatments. We specifically assessed the number of responders defined by a
53 decreased of the CLE Disease Area and Severity Index activity of at least 50% (CLASI-50) at
54 6 months (M6)⁴.

55 We included 16 patients (15 women, median age at diagnosis 48 [range 19-65]) (**Table 1**).
56 Thirteen patients had associated SLE and 3 had isolated CLE. Belimumab was administered
57 intravenously at 10mg/kg every 2 weeks for three doses and then monthly. Median duration
58 of lupus was 18 years [range 3-38] and patients previously failed a median of 6.5 systemic
59 treatments [range 3-11] before belimumab. Most patients (n=12, 75%) had chronic CLE. The
60 median number of belimumab infusions was 8 [5-16]. No change in treatments that could
61 impact CLE activity was noted in the 3 months prior to belimumab initiation. At M6 (or M5,
62 n=2 patients), CLASI-50 was observed in 8 patients (50%) and 3 (19%) had a complete
63 response. A trend for an overall improvement of CLASI activity was observed (10 [range 4-
64 42] versus 7.5 [0-30], p=0.07) (**Figure 1**). CLASI-50 was observed more frequently in CLE
65 patients with Fitzpatrick phototype IV-VI than II-III (7/9 (78%) vs 1/7 (18%) p=0.04) and
66 baseline CLASI tended to be lower in patients with complete response than without (6 [range
67 5-9]) versus 15 [4-42], p=0.09). Among SLE patients with cutaneous response to belimumab,

68 a decrease of 4-points of SLEDAI was noted in 2/6 (33%) and a decrease $\geq 25\%$ from
69 baseline prednisone dose was noted in 4/5 (57%). No adverse events were recorded. At the
70 last follow-up belimumab was stopped in 5/8 patients with initial response because of a
71 persistent activity.

72 To our knowledge, only 2 patients with Chronic CLE treated with belimumab have been
73 previously reported². In our study, 50% of patients had CLE response although an overall
74 statistical improvement was not observed. This suggests that belimumab may be beneficial in
75 some patients mostly with mild persistent activity and phototype IV-VI. Interestingly, a
76 clinical response was observed in the 3 patients with isolated CLE which supports the results
77 of a recent ex-vivo study on the role of BLYS in CLE pathogenesis⁵. The main limitations of
78 this study are the small number of patients and its retrospective nature. Moreover, we
79 included patients with very severe and refractory CLE which could explain the limited
80 response. The role of belimumab as second-line treatment of CLE could therefore be
81 investigated.

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Table 1. Characteristics of the 16 included lupus patients

Patient No	Age(y)/Sex/Phototype*	Active smoking	CLE subtypes	CLASI baseline/M6	Cutaneous Response	Systemic involvement	Previous systemic lines (N)	Associated treatments	Number of infusions	Withdrawal/Reason
1	43/F/IV	0	SCLE/tumidus	17/7	PR	Articular, LN, Hematological	4	TCI, HCQ, GC, MMF	16	Yes/good improvement
2	58/F/II	+	Tumidus	9/5	MR	0	3	HCQ, MTX	13	Yes/persistent activity
3	33/F/V	0	ACLE/DLE	15/15	Failure	Articular, LN	6	HCQ, GC, MTX	8	Yes/failure
4	60/M/IV	+	SCLE	6/0	CR	0	5	AZA, GC	9	Yes/CR
5	28/F/V	0	ACLE/DLE	15/5	PR	Articular	3	HCQ, GC	9	Yes/loss of follow-up
6	63/F/II	0	SCLE	18/30	Failure	LN	7	CQ, GC, MTX	6	Yes/failure
7	19/F/V	0	ACLE/DLE	9/0	CR	Articular, serositis, LN	3	HCQ, GC, MMF	15	No
8	65/F/IV	0	DLE	6/3	PR	Articular, LN, Hematological	8	HCQ, GC	10	Yes/persistent activity
9	51/F/III	0	DLE	20/24	Failure	Articular, LN	9	TCS	7	Yes/Failure
10	36/F/II	+	DLE	11/11	Failure	Articular	8	HCQ, lenalidomide	6	Yes/failure
11	53/F/II	0	DLE	8/4	PR	Articular, serositis, hematological	7	HCQ, GC, MMF	8	Yes/persistent activity
12	46/F/II	0	SCLE/DLE	4/8	Failure	Articular	5	HCQ, GC, lenalidomide	8	Yes/failure
13	29/F/IV	+	DLE	5/0	CR	Articular, serositis	11	HCQ, GC, MMF	5	Yes/CR
14	51/F/VI	+	DLE	42/18	PR	0	10	HCQ, alitretinoin, lenalidomide	5	Yes/persistent activity
15	61/F/III	0	DLE	8/8	Failure	Articular, hematological	4	HCQ, GC, dapsone	7	Yes/failure
16	37/F/VI	0	DLE	18/14	MR	Hematological, serositis	8	HCQ, GC	6	Yes/persistent activity

* According to Fitzpatrick, CLE: cutaneous lupus erythematosus, CLASI: cutaneous lupus erythematosus disease area and severity index, PR: partial response (decreased of the CLASI activity of at least 50%), MR: minimal response (decrease of CLASI activity of 4 points or 20%, which has been shown to be a reliable meaningful clinical improvement⁴), CR: complete response, SCLE: subacute CLE, ACLE: acute CLE, DLE: discoid lupus erythematosus, TCI: topical calcineurin inhibitor, HCQ: hydroxychloroquine, GC: oral glucocorticoids, MMF: mycophenolate mofetil, MTX: methotrexate, AZA: azathioprine; CQ: chloroquine, TCS: topical corticosteroids. No significant differences were observed

between patients with or without partial response regarding smoking status, CLE subtype (DLE vs other subtypes) and the number of previous failed treatments.

118 **Figure Legend**

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120 **Figure 1. Before and after photograph of a belimumab CLE responder. Variation of cutaneous lupus erythematosus disease area and**
121 **severity index (CLASI) before and after 6 months in lupus patients treated with belimumab for refractory skin disease. CLASI changes**
122 **for 16 patients (black bars) and median RCLASI improvement (red bars) before and after 6 months of belimumab treatment. Two patients**
123 **stopped belimumab after 5 infusions and therefore we used CLASI activity after 5 months**

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