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Dear Editor,

Anifrolumab, a human monoclonal antibody that binds IFN-I receptor subunit 11, has been approved for the treatment of systemic lupus erythematosus (SLE). Clinical trials have shown that anifrolumab is effective in cutaneous lupus erythematosus (CLE) associated with SLE 1,2. A few case reports have suggested the efficacy of anifrolumab in refractory CLE 3. However, its real-life efficacy in the setting of CLE refractory to standard therapies including thalidomide, lenalidomide and belimumab has not been assessed using validated disease activity instruments 4. This national multicenter prospective study enrolled SLE patients with biopsy-proven active CLE despite optimal treatment with failure of at least three currently available CLE treatments, including belimumab (mandatory to be eligible in the early access program in France). Of note, all patients had to be fully vaccinated against COVID-19 before starting anifrolumab. Anifrolumab (300 mg intravenously every 4 weeks) was started between August 2021 and May 2022, and the patients were followed up for a minimum of 16 weeks. The primary outcome was the proportion of partial response (PR) at week 16 defined by a decrease of CLE Disease Area and Severity Index activity of at least 50% (CLASI-A 50)1,4. SLE activity (SELENASLEDAI score5) and adverse events were also assessed (Supplementary Methods). Analyses were performed using the JMP 15 software (SAS

Institute, Cary, NC, USA). The study protocol was approved by our local IRB (CEEI/IRB 22-946). Eleven women were included in the study. The detailed characteristics at baseline are presented in Table 1. Before starting anifrolumab, the median number of systemic treatment lines for CLE per patient was 6 (3-9). CLASI-A 50 at week 16 was reached by the 11 patients. The median CLASI activity decreased from 15 (4-35) at baseline to 4 (0-19) at week 4 (p=0.001) and 2 (0-13) at week 16 (p<0.001) *(Figure 1)*. The median time to reach CLASI-A 50 was one month (95% CI 1-3*) (Supplementary Figure 1).* Seven patients received additional infusions after week 16, up to week 40 for one patient. All patients showed sustained improvement in CLASI activity. A complete response (CLASI-A=0) was observed in 6 patients (54%). No significant variation in the median CLASI damage was observed *(Supplementary Figure 2)*. The median SELENA-SLEDAI score significantly decreased from 8 (4-22) at baseline to 4 (0-10) at week 16 (p=0.002) *(Supplementary Figure 2)*, and all 5 patients with baseline articular involvement had disappearance of their clinical symptoms. The median dose of prednisone decreased from 10 mg/day (0-15) to 5 mg/day (0-10). Eight (73%) patients had at least one AEs, with a total of 10 AEs *(Supplementary Table 1*). No patient discontinued anifrolumab permanently because of an AE. Infectious AEs included two non-severe COVID-19 cases with spontaneous recovery (grade 1) (for which anifrolumab infusion was delayed for 2 weeks), one herpes zoster, one case of worsening preexisting palmar warts, and one case of mucosal candidiasis. The main limitations of this study are its limited sample size and follow-up duration. Overall, anifrolumab is a promising therapeutic option for refractory CLE.

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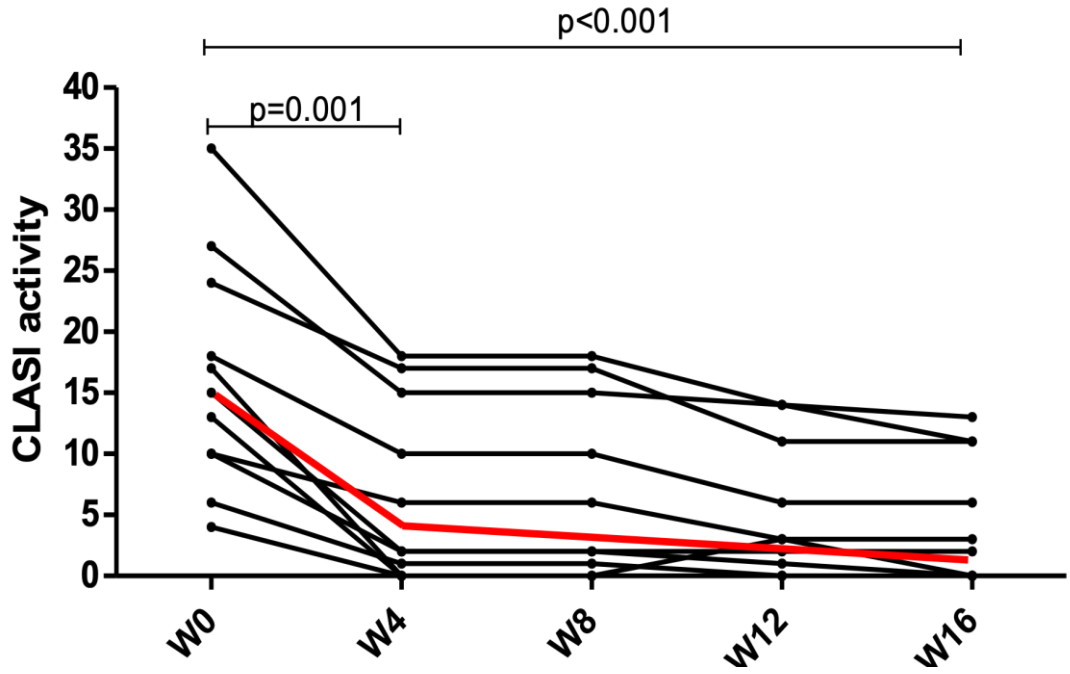

Figure 1 legend : CLASI activity in 11 patients before and at weeks 4, 8, 12, and 16 of anifrolumab treatment. Black solid circles represent individuals. The red bar indicates the median values calculated only between weeks 0 and 16. P-values were calculated using the Mann-Whitney U test. $p<0.05$ was considered significant. W, week. Anifrolumab exposure after week 16 is also reported. CLE subtypes of patients achieving complete response were both subacute and localized DLE n=3, subacute and chilblain lupus n=1, localized DLE n=1 and disseminated DLE n=1

Table 1: Patient characteristics and disease parameters SLE patients (n = 11)

Socio-demographic features	
Age at baseline, median (range)	35 (19-50)
Phototype:	
- I-IV	7 (64)
- V-VI	4 (36)
Female sex	11 (100)
Active smoking at last follow-up	4 (36)
SLE duration, years, median (range)	12 (3-23)
Historical treatment and belimumab history	
- Hydroxychloroquine	11 (100)
- Chloroquine	1 (9)
- Glucocorticoids	10 (91)
- Methotrexate	8 (73)
- Thalidomide or lenalidomide	11 (100)
- Other immunosuppressant or immunomodulatory drug*	8 (73)
Previously treated with Belimumab	11(100)
Median duration of belimumab (month), median (range)	24 (2-72)
Belimumab efficacy:	
- Partial response and secondary relapse	5 (45)
- Primary failure	6 (55)
Median number of systemics before starting anifrolumab, median (range)	6 (3-7)
Active CLE features at the time of anifrolumab initiation	
Active cutaneous subtypes at baseline:	
- Discoid CLE	10 (91)
- Subacute CLE	4 (36)
- Chilblains lupus	1 (9)
- More than one subtype**	4 (36)
Specific topography of CLE	
- Scalp discoid lupus	6 (54)
- Digital involvement	7 (64)
- Mucosal involvement	6 (54)
Treatments continued with anifrolumab	
Hydroxychloroquine	10 (91)
Chloroquine	1 (9)
Systemic glucocorticoids	9 (82)
Systemic glucocorticoids dose (mg), median (range)	10 (2-15)
Methotrexate	2 (18)
Mycophenolate mofetil	2 (18)
Thalidomide or lenalidomide	2 (18)
Baseline CLE and SLE activity and damage at the time of anifrolumab initiation	
CLASI activity at baseline, median (range)*	15 (4-35)
CLASI damage at baseline, median (range)*	6 (0-25)
SLEDAI at baseline, median (range)**	8 (4-22)

Values are expressed as n (%) unless stated otherwise. *Mycophenolate mofetil (n=4), Azathioprine (n=4), Cyclophosphamide (n=1), Rituximab (n=3) ** All patients with subacute lupus had another CLE subtype including discoid lupus (n=3) and chilblain lupus (n=1)" CLASI: CLE Disease Area and Severity Index, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index