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PAPER

Fumaric acid ester treatment in cutaneous lupus erythematosus (CLE): a prospective, open-label, phase II pilot study

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Objective: The aim of the study was to assess the efficacy and safety of fumaric acid esters (FAEs) in patients with cutaneous lupus erythematosus (CLE). **Methods:** In this 24-week, prospective, open-label, phase II pilot study, 11 patients with CLE, refractory to topical corticosteroids, were included. The primary endpoint of the study was the evaluation of the efficacy of FAEs after 24 weeks of treatment as assessed by the Revised Cutaneous Lupus Disease Area and Severity Index (RCLASI). **Results:** Compared to baseline, significant improvement in the mean total RCLASI activity score and the mean RCLASI activity score for skin lesions was observed in week 12 ($p = 0.002$, $p = 0.002$, respectively) and in week 24 ($p = 0.009$, $p = 0.009$, respectively). Most common adverse events included abdominal cramps and headache. **Conclusions:** FAEs could be an alternative and safe treatment in patients with therapy-refractory CLE; however, randomized controlled trials are warranted to evaluate the efficacy and safety of FAEs in this disease. *Lupus* (2016) **0,** 1–8.

Key words: Cutaneous lupus erythematosus; alternative treatment; fumaric acid esters; RCLASI; clinical trial

Introduction

Lupus erythematosus (LE) is an autoimmune disease with a broad spectrum of clinical manifestations ranging from lesions primarily confined to the skin (cutaneous lupus erythematosus, CLE) to others that involve one or more vital internal organs (systemic lupus erythematosus, SLE).[1] Although several agents are licensed for SLE and other immunological diseases, no medication has been approved specifically for the treatment of CLE. Therefore, 'off-label' topical and systemic agents are applied in most patients with CLE based on expert opinions.[2,3] The first-line treatment for disfiguring and widespread skin manifestations in patients with CLE are antimalarial agents, such as hydroxychloroquine.[2] However, there are only single further therapeutic options for patients with therapy-refractory CLE, resulting in a high need for new therapeutic agents in this disease.[4,5]

Fumaric acid esters (FAEs), namely Fumaderm®, were approved in Germany for severe psoriasis vulgaris in 1994, and an extended license was granted in Germany for moderate to severe psoriasis vulgaris in 2008.[6–8] The pharmacologically effective molecules among the FAEs are dimethylfumarate (DMF) and monoethylfumarate (MEF). Recently, the efficacy of DMF as a sole active ingredient (Tecfidera®) has also been demonstrated in relapsing multiple sclerosis[9] and was approved in 2013 for this indication. Different modes of actions of DMF are discussed in the scientific community: one described mechanism is based on the inhibition of the activity of the transcription factor nuclear factor (NF)-κB and the secretion of proinflammatory cytokines by T-cells.[10,11] Several additional effects of FAEs have been suggested, such as the inhibition of keratinocyte proliferation and the suppression of adhesion molecules.[10,12,13] Such immunomodulatory

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mechanisms are also involved in the pathogenesis of CLE. Therefore, it can be hypothesized that FAEs might also have positive therapeutic effects in this disease.

To date, only three case reports on the treatment of FAEs in patients with CLE have been published by Balak and Thio, Klein, and Tsianakas and colleagues,[14–16] describing the efficacy of FAEs in this disease. Here, we report the results of an open-label, prospective, phase II pilot study including the evaluation of the efficacy and safety of FAEs in patients with CLE.

Materials and methods

Study design

This explorative, phase II pilot study was performed at the Department of Dermatology, University of Muenster, Germany. Approval from the Ethics Committee in Muenster, Germany (date: March 15, 2011), and the Federal Institute for Drugs and Devices (BfArM, EudraCT No. 2010-023645-29) was obtained prior to the study, which was conducted according to the ethical guidelines of the Declaration of Helsinki and performed according to the Good Clinical Practice (GCP) guidelines. Main inclusion criteria were age between 18 and 70 and a clinically and histologically confirmed diagnosis of CLE refractory to topical corticosteroids. However, patients were not allowed to receive topical corticosteroids within 14 days or systemic immunosuppressives four weeks prior to screening. Moreover, initiation or change in the dose of any current systemic medication for the treatment of CLE prior to the study was not allowed. Main exclusion criteria were lymphopenia (<500/µl) and severe systemic manifestations. Study duration was 24 weeks of treatment with a follow-up period of four weeks.

Patients

After written informed consent had been obtained, 11 patients (seven female, four male) with the clinical and histological diagnosis of CLE were included in the study between July 2011 and October 2013. Ten patients had been diagnosed with discoid lupus erythematosus (DLE), and one patient presented with the main diagnosis of subacute cutaneous lupus erythematosus (SCLE) and a single DLE lesion. (Table 1). The mean age of the patients ranged from 31 to 60 years (mean ± SD 47 ± 9.3 years). All patients fulfilled a maximum of three criteria of the American College of Rheumatology (ACR) for the classification of SLE, respectively.[17] Serological laboratory investigations revealed that antinuclear antibodies (ANA; HEp-2 cell test) were positive (titer >1:160) in eight of 11 patients and anti-Ro/SSA antibodies in four of 11 patients. Testing for anti-La/SSB antibodies, anti-Sm antibodies and anti-double-stranded DNA (anti-dsDNA) antibodies was negative in all patients. All patients completed the study, although two patients (numbers 2 and 10) missed visit 6 (week 12).

Outcome measures

The Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI) was designed to score the activity and damage of the disease, taking into account anatomical regions

Table 1 Characteristics of patients included in the study

Patient number	*Diagnosis*	*Age (years)/Sex*	*Duration of disease (years)*	*Positive serological features*	*ACR criteria ever*
1	DLE	52/F	4	ANA	Discoid lesions, Photosensitivity, ANA
2	DLE	48/F	14	ANA, anti-Ro/SSA	Discoid lesions, Photosensitivity, ANA
3	DLE	38/F	7	ANA, anti-Ro/SSA	Discoid lesions, Photosensitivity, ANA
4	SCLE[a]	60/M	7	ANA, anti-Ro/SSA	Discoid lesions, Photosensitivity, ANA
5	DLE	57/F	5	ANA	Discoid lesions, Photosensitivity, ANA
6	DLE	50/F	21	ANA, anti-Ro/SSA	Discoid lesions, Photosensitivity, ANA
7	DLE	31/M	8	–	Discoid lesions, Photosensitivity
8	DLE	43/M	6	ANA	Discoid lesions, Photosensitivity, ANA
9	DLE	55/F	5	–	Discoid lesions, Photosensitivity
10	DLE	48/F	27	–	Discoid lesions, Photosensitivity
11	DLE	35/M	6	ANA	Discoid lesions, Photosensitivity, ANA

[a]Main diagnosis SCLE, solitary lesion of DLE on the nose.
DLE: discoid lupus erythematosus; F: female; M: male; ANA: antinuclear antibodies (HEp-2 cells); SCLE: subacute cutaneous lupus erythematosus; ACR: American College of Rheumatology.

Table 2 Adverse events (AEs) noted by patients included in the study[a]

Patient number	*Adverse events*	*Maximum dose of Fumaderm®/day*
1	Constipation, abdominal cramps, headache, diarrhoea, vomiting	1 tablet
2[b]	Headache, tachycardia	4 tablets
3	Meteorism	6 tablets
4	Abdominal pain	6 tablets
5	–	4 tablets
6[b]	Abdominal cramps, diarrhoea	1 tablet
7	Headache	6 tablets
8	–	3 tablets
9	Erythema/Flush, diminished appetite, abdominal pain, dizziness	4 tablets
10	Diarrhoea, abdominal cramps, nausea, tachycardia	5 Tablets
11	Erythema/Flush, abdominal cramps, increased transaminases	6 Tablets

[a]Only AEs with a reasonable causal relationship to the study medication are listed.
[b]Temporary discontinuation of study treatment (Fumaderm®) for nine days (patient number 1) and 14 days (patient number 6) due to AEs.

(e.g. face, chest, arms) as well as morphological aspects (erythema, scale/hyperkeratosis, oedema/infiltration, subcutaneous nodule/plaque, dyspigmentation, scarring/atrophy) of skin lesions, as previously described.[24,18] In the present study, the RCLASI scores (i.e. the total RCLASI activity score, the RCLASI activity score for skin lesions and the total RCLASI damage score) were evaluated by the investigator at baseline, after 12 and 24 weeks of treatment and after the follow-up period in week 28. Moreover, the patients were assessed by the Visual Analogue Scale (VAS) and the Patient Assessment of Global Improvement (PAGI) at baseline and after 12 and 24 weeks of treatment and after the follow-up period in week 28.

Endpoints

The primary endpoint of the study was to evaluate the efficacy of FAEs in the treatment of CLE by applying the 'RCLASI 50 skin' (a reduction of at least 50% of the RCLASI activity score for skin lesions) after 24 weeks. Secondary endpoints were to analyse the efficacy of FAEs after 12 weeks of treatment as evaluated by the 'RCLASI 50 skin', to evaluate the efficacy of FAEs after 12 and 24 weeks of treatment as evaluated by the 'RCLASI 50 total' (a reduction of at least 50% of the total RCLASI activity score), and the proportion of failures after 12 and 24 weeks of treatment. Failure was defined as a reduction of less than 25% in the total RCLASI activity score compared to the baseline value. Further secondary endpoints included the evaluation of the PAGI and the VAS. Laboratory test value abnormalities were reported as adverse events (AEs) if they were supposed to be associated with known side effects of the study medication (Table 2).

Table 3 Dosage scheme for Fumaderm® initial/Fumaderm®[a]

Week	*Number of tablets per day*	*Agent*
1	1	Fumaderm® initial
2	2	
3	3	
4	1	Fumaderm®
5	2	
6	3	
7	4	
8	5	
9–24	6	

[a]Modified after Pathirana et al.[6]

Intervention

Following the established scheme in the treatment of psoriasis vulgaris (Table 3), study treatment was started with one enteric-coated tablet of Fumaderm® initial (Biogen, Ismaning, Germany; 30 mg dimethylfumarate and 75 mg monoethylfumarate salts) per day and was stepwise increased weekly (during nine weeks) up to six enteric-coated tablets Fumaderm® (120 mg dimethylfumarate and 95 mg monoethylfumarate salts) per day, as tolerated by the patient.[6] Estimation of tolerability was based on AEs reported by the patient and/or observed by the physician. If AEs related to study treatment (e.g. abdominal cramps, diarrhoea or headache) occurred, the dosage was decreased to the previously tolerated dose or treatment was temporarily discontinued until the AEs resolved (Table 2).

Statistical analysis

Descriptive statistical analyses were performed on all efficacy and safety parameters. If applicable,

inferential analyses were carried out by means of Student's *t*-tests for paired data. As this study was an exploratory study, all inferential statistics were exploratory (hypotheses generating), not confirmatory, and were interpreted accordingly; i.e. *p* values are interpreted as a metric weight of evidence against the respective null hypothesis of no effect/no difference. No adjustment for multiple testing was performed.

Concomitant treatment

All patients were advised to continue the application of sunscreens with a high sun protection factor (>50). Drugs with a photosensitizing potential, drugs known to induce CLE, drugs with nephrotoxic potential and immunosuppressives were not allowed during the study. Treatment with other systemic agents was permitted, if the drug had been taken prior to the study (time depending on drug class) and treatment dosage was not changed during the study (i.e. antimalarial agents). Patients requiring additional therapy with topical steroids for more than four weeks, other topical treatment or systemic treatment due to lack of efficacy would have been considered as treatment failures.

Results

Efficacy of FAEs on disease severity as evaluated by total RCLASI activity score, RCLASI activity score for skin lesions and total RCLASI damage score

At baseline, the total RCLASI activity score was 15.5 ± 5.3 (mean ± SD), and the RCLASI activity score for skin lesions was 14.8 ± 5.4 (mean ± SD) (Figure 1(a) and (b)). After 12 weeks of treatment, significant decreases in the total RCLASI activity score and the activity score for skin lesions compared to the scores at baseline were observed (mean ± SD 9.9 ± 4.9, $p = 0.002$; mean ± SD 9.4 ± 5.2, $p = 0.002$, respectively; $n = 9$). After 24 weeks of treatment with FAEs, the total RCLASI activity score and the RCLASI activity score for skin lesions were still significantly decreased compared to the scores at baseline (mean ± SD 10.1 ± 6.6, $p = 0.009$; mean ± SD 9.5 ± 6.1, $p = 0.009$, respectively; $n = 11$). Compared to the scores at baseline, the total RCLASI activity score and the RCLASI activity score for skin lesions at week 28 (''Follow-Up'') were still significantly decreased (mean ± SD 10.5 ± 4.6, $p = 0.01$; mean ± SD 9.9 ± 4.2, $p = 0.01$, respectively; $n = 11$).

The total RCLASI damage score at baseline was 5.7 ± 2.9 (mean ± SD). After 12, 24, and 28 weeks of treatment, the total RCLASI damage score was reduced (mean ± SD 4.4 ± 1.7; mean ± SD 4.9 ± 3.6; mean ± SD 4.2 ± 3.7, respectively) compared to the score at baseline. However, the differences were not significant.

Efficacy of FAEs on disease severity as evaluated by patient assessment scores (VAS for itch and pain, PAGI)

The VAS scores for itch and pain significantly decreased between baseline (mean ± SD 5.0 ± 3.2 and 3.4 ± 3.4, respectively) and the visit after 12 weeks of treatment with FAEs (mean ± SD 2.1 ± 1.8, $p = 0.03$, mean ± SD 2.0 ± 2.7, $p = 0.05$, respectively; $n = 8$). After 24 weeks of treatment, the VAS scores for itch and pain were lower compared to baseline (mean ± SD 3.3 ± 2.7 and 2.4 ± 2.2, respectively; $n = 10$), but the differences were not statistically significant.

The mean PAGI at baseline was -0.6 ± 0.7 (mean ± SD). Compared to baseline, the PAGI score was observed to be significantly improved after 12 weeks of treatment (mean ± SD 1.4 ± 0.7, $p = 0.0003$; $n = 9$) and after 24 weeks of treatment (mean ± SD 1.3 ± 0.8, $p = 0.0007$; $n = 10$). In single cases, the VAS and the PAGI were not filled in by all patients, explaining the different numbers of the analysed data.

Efficacy of FAEs with regard to disease duration

The mean duration of disease in the CLE patients was 10.0 ± 7.5 years (range: 4.0–27.0 years). No clear relation between the efficacy of FAEs and disease duration of patients with CLE was observed in the study. Of 11 patients, four with a disease duration ranging from five to 27 years (numbers 7, 9, 10, 11) did not respond to treatment with FAEs (Table 1, Table 4); remarkably, three of these four patients had concomitant therapy with antimalarials and two of them received the maximum dose of FAEs (numbers 7 and 11). In contrast, treatment with FAEs resulted in a decrease of the RCLASI activity score for skin lesions from 18 points (baseline) to 11 points (week 24) in a patient with a disease duration of six years (number 8), and the RCLASI activity score for skin lesions decreased from 16 points (baseline) to 8 points (week 24) in a patient with a disease duration of 21 years (number 6).

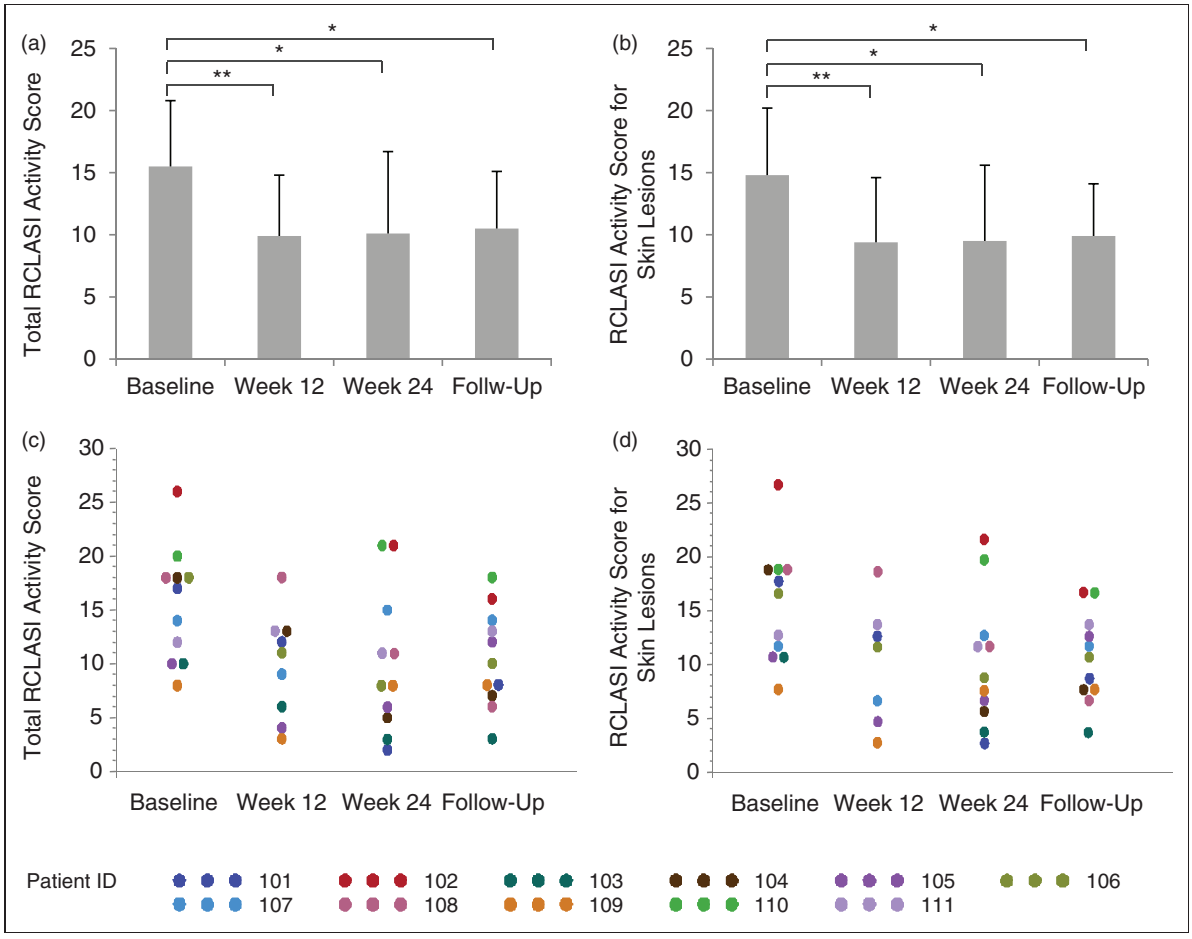

Figure 1 (a) Mean total RCLASI activity score of the included 11 patients with CLE at baseline, week 12, and week 24 of treatment with FAEs and at follow-up. (b) Mean RCLASI activity score for skin lesions of the included 11 patients with CLE at baseline, week 12, and week 24 of treatment with FAEs and at follow-up. $*p < 0.05$, $**p < 0.005$. (c) Individual values of the total RCLASI activity score of the included 11 patients with CLE at baseline, week 12, and week 24 of treatment with FAEs and at follow-up. (d) Individual values of the RCLASI activity score for skin lesions of the included 11 patients with CLE at baseline, week 12, and week 24 of treatment with FAEs and at follow-up. RCLASI: Revised Cutaneous Lupus Disease Area and Severity Index; CLE: cutaneous lupus erythematosus; FAEs: fumaric acid esters.

Efficacy of FAEs with regard to gender, disease subtypes, and antibodies

Of the included seven female DLE patients, five showed a good response to treatment with FAEs, while the skin lesions of only one of the three male DLE patients improved within 24 weeks. Because of the small sample size and the prevalence of females, no further correlation of gender and efficacy of FAEs was performed. In six of the 10 DLE patients, treatment with FAEs resulted in an improvement of skin lesions, and four DLE patients did not or only marginally responded to treatment (numbers 7, 9, 10 and 11; Figure 1(c), (d), Table 4). The patient with the main diagnosis of SCLE and a solitary DLE lesion (number 4) showed a very good response to treatment with FAEs: the RCLASI activity score for skin lesions decreased from 18 points (baseline) to 13 points (week 12) and further decreased to five points (week 24). Interestingly, the SCLE lesions of the back resolved completely (Figure 2(a), 2(b)), whereas the solitary DLE on the nose resulted in the described decrease of five points. As 10 patients with DLE and only one patient with SCLE were included in the study, a comparison of the efficacy of FAEs in different disease subtypes could not be performed. Interestingly, seven of eight patients with positive ANA showed an improvement in the RCLASI activity score for skin lesions, while in only one patient (number 11) who presented with positive ANA, the RCLASI activity score for skin lesions decreased only from 12 points (baseline) to 11 points (week 24). However, a possible correlation between the incidence of ANA and the efficacy of FAEs has to be evaluated in further trials.

Table 4 Treatment and scores of patients included in the study

Patient number/Sex	*Continued concomitant treatment for CLE*[a]	*Total RCLASI activity (baseline)*	*Total RCLASI activity (week 24)*	*RCLASI activity skin (baseline)*	*RCLASI activity skin (week 24)*	*VAS itch (baseline)*	*VAS itch (week 24)*	*VAS pain (baseline)*	*VAS pain (week 24)*	*PAGI (baseline)*	*PAGI (week 24)*
1/F	–	17	2	17	2	6	0	6	0	–1	3
2/F	–	26	21	26	21	10	7.5	0	4.5	–1	1
3/F	Antimalarials (7 y, 3 m)	10	3	10	3	–	2	–	0	–1	2
4/M	–	18	5	18	5	5	4	2	2	–1	2
5/F	–	10	6	10	6	3	0	1	0	0	1
6/F	–	18	8	16	8	2	2	1	2	–1	–
7/M	Antimalarials (8 m)	14	15	11	12	6	4	8	5	–1	1
8/M	Antimalarials (3 y)	18	11	18	11	5	5	1	2.5	–1	0
9/F	Antimalarials (5 y, 5 m)	8	8	7	7	8	5	8	5	–1	1
10/F	–	20	21	18	19	8	7	7	5	1	1
11/M	Antimalarials (5 y, 6 m)	12	11	12	11	0	0	0	0	0	1

[a]Duration of treatment prior to study inclusion is listed; y: years; m: months.
F: female; M: male; CLE: cutaneous lupus erythematosus; RCLASI: Revised Cutaneous Lupus Disease Area and Severity Index; VAS: Visual Analogue Scale; PAGI: Patient Assessment of Global Improvement.

Figure 2 (a) Subacute cutaneous lupus erythematosus (SCLE). Erythematous papules and annular plaques with polycyclic confluence of lesions on the upper back of patient 4 at baseline. (b) Complete resolution after treatment with fumaric acid esters (FAEs) (picture taken at week 24).

Safety

The most common AEs with a reasonable causal relationship to study treatment were abdominal cramps and headache, followed by diarrhoea, tachycardia, abdominal pain, and erythema/flush (Table 2). In only one patient (number 11), increased transaminases were observed; but on reduction of the study treatment dose, the values normalized. No further laboratory abnormalities, such as leucopenia or lymphopenia, occurred during study treatment. Two serious adverse events (SAEs) occurred during the study (lumbar discus prolapse and reimplantation of urinary bladder pacemaker), but were not considered causally related to study treatment.

Discussion

To our knowledge, this is the first prospective, exploratory phase II study evaluating the efficacy and safety of FAEs in patients with CLE. The mean total RCLASI activity score and the mean

RCLASI activity score for skin lesions decreased significantly between baseline and week 12 and between baseline and week 24, respectively (Figure 1(a), (b)). However, the endpoints of the 'RCLASI 50 total' and the 'RCLASI 50 skin' were not accomplished; a reduction of at least 50% of the mean total RCLASI activity score and the mean RCLASI activity score for skin lesions would have been expected a reduction from 15.5 points (baseline) to 7.7 points (week 24) and from 14.8 points (baseline) to 7.4 points (week 24), respectively. In week 24, however, the mean total RCLASI activity score was 10.1 and the mean RCLASI activity score for skin lesions was 9.5. The 'RCLASI 50' – according to the Psoriasis Area and Severity Index (PASI) 50, which is usually applied in clinical trials of psoriasis vulgaris[19] – was applied for the first time in this study; therefore, no experience exists on this type of index definition as an endpoint. Moreover, DLE was the most frequent subtype included in the study, which is considered one of the most therapy-refractory CLE subtypes with a chronic course of the disease.[20] Therefore, the application of the 'RCLASI 50' has to be reconsidered in future trials including patients with different disease subtypes, preferentially during the early course of the disease. The results of our pilot study show no clear relation between duration of disease in CLE and efficacy of FAEs.

Recently, our group published preliminary data on one of the included DLE patients (number 1).[16] To our knowledge, the application of FAEs in CLE has been described in only two further case reports. In 2011, Balak et al.[14] reported on two patients with different subtypes of CLE, which were treated with FAEs with increasing doses of up to six tablets Fumaderm® per day. The first patient, a therapy-refractory 35-year-old female with LE tumidus, demonstrated a complete resolution of lesions within three months of treatment with FAEs. In a 24-year-old patient with erythematous scaly plaques, Raynaud's phenomenon, alopecia and oral ulcers, who was diagnosed as SLE, refractory to prednisone, hydroxychloroquine, and cyclosporine, the combination treatment with FAEs and 10 mg prednisone resulted in improvement of the skin lesions within three months. Because of planned pregnancy, FAEs were stopped; retreatment had an equally good effect within three months. Side effects in these patients included nausea, diarrhoea, abdominal cramps, mild leucopenia, transient proteinuria, tiredness, and pruritus. Klein et al.[15] reported a 42-year-old male patient with DLE who was therapy-refractory to hydroxychloroquine monotherapy; four months of combination with FAEs resulted in stable disease. In the present study, two of five DLE patients receiving FAEs in combination with continued antimalarials responded to treatment, while three patients did not show any improvement of skin lesions. This might be explained by the fact that these patients with the chronic subtype of DLE, not responding to antimalarial agents, are highly therapy resistant.

The most frequently observed AEs in this study were abdominal cramps, headache, diarrhoea, tachycardia, abdominal pain, and erythema/flush, which is in correlation with the manufacturers' prescribing information and the AEs described in long-term trials in psoriasis vulgaris.[21] Similar AEs were described in the publications by Balak and Klein.[14,15] Therefore, the results of the previous case reports support the data on the safety of FAEs in this study. However, limitations of the present study are the small sample size and the high prevalence of therapy-refractory DLE patients with a chronic course of the disease.

In the present study, off-label treatment with FAEs reduced the activity of skin lesions in seven of 11 patients including one SCLE patient and six patients with long-standing therapy-refractory DLE. In accordance with findings from previous long-term studies in psoriasis vulgaris, no significant AEs with a reasonable causal relationship to the study medication occurred. Therefore, FAEs could be a safe and efficient treatment option in patients with CLE who are refractory to antimalarials or in whom antimalarials are contraindicated. However, the efficacy of FAEs needs to be confirmed in randomized controlled trials, including more patients with SCLE and other disease subtypes.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs

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