RESEARCH LETTER

Line-field Confocal Optical Coherence Tomography Detects Subclinical Disease Activity in Atopic Dermatitis during Treatment with Pimecrolimus: An Intrapatient, Controlled Study

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To the Editor,

Atopic dermatitis (AD) is a common chronic, remitting-relapsing inflammatory skin disease. AD flares are frequent, and their cause remains a matter of debate (1). Pimecrolimus is a steroid-sparing, anti-inflammatory agent that has been shown to be effective in the treatment of acute AD in infants, children and adults (2).

Line-field confocal optical coherence tomography (LC-OCT) is a new noninvasive imaging technique that has been recently introduced for the diagnosis of several cutaneous disorders including AD (3–5). In acute AD, LC-OCT allows the *in vivo* recognition of histopathological clues/hallmarks such as spongiosis, vesiculation, and inflammatory cells (3). A recent study explored its usefulness in monitoring the response to treatment in patients with severe AD receiving dupilumab (6). Moreover, LC-OCT combined with algorithms based on artificial intelligence (AI) has been applied to extract quantitative parameters related to epidermal architecture (e.g. layer thickness and undulation) and cellular-level markers (including nuclear volume, shape and homogeneity) during both flare-ups and remission phases in patients treated with topical corticosteroids (7).

The aim of this study was to assess whether clinical changes and/or lesion clearing correlate with LC-OCT findings in two cohorts of young and elderly patients with AD treated with pimecrolimus 1% cream or moisturizer.

In this monocentric, intrapatient controlled study, 10 young (age range: 7–15 years) and 10 elderly (age range: 65–80 years) patients of both sexes, affected by mild-to-moderate acute AD, were enrolled. For each patient, two symmetrical target lesions were selected. The patients were instructed to apply pimecrolimus 1% cream in one lesion and a moisturizer (same for all, containing ceramides) to the contralateral lesion twice daily for 4 weeks. Treatment efficacy was clinically and instrumentally evaluated after 2 (T1) and 4 (T2) weeks of treatment, and clinical rating was performed using a 5-point Investigator Global Assessment (IGA) scale (-1=worsening; 0=no change; 1=mild improvement; 2=marked improvement; 3=clearing). LC-OCT evaluated the presence or absence of the AD pattern (spongiosis, vesiculation, and inflammatory cells) at each time point.

The results are shown in **Table I**. Considering the target lesions treated with pimecrolimus 1% cream, a time-dependent improvement in clinical parameters and LC-OCT outcomes was observed over time in both the young and elderly groups. In detail, at T1, clearing was clinically observed in 8 cases, with LC-OCT showing persistence of the AD pattern in 5 of them (**Fig. 1**); at T2, clearing was observed in 15 cases both clinically and by LC-OCT, and a marked improvement in the five remaining cases showing at LC-OCT persistence of the AD pattern. Lesions treated with moisturizer alone did not show relevant clinical and/or LC-OCT modifications during follow-up visits (Table I).

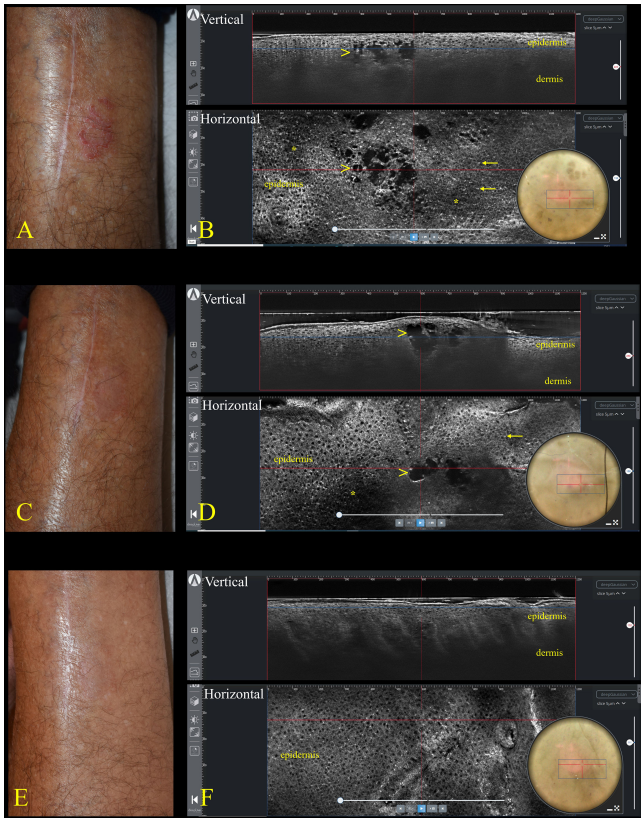

Fig. 1. (A) Eczematous plaque of the leg in a 65-year-old man affected by atopic dermatitis. (B) Vertical and horizontal LC-OCT showing the presence of spongiosis (asterisks), intraepidermal vesicles (arrowheads) and small, bright, inflammatory cells (arrows); round insert: dermoscopy of the examined area. (C) clinical clearing; (D) LC-OCT showing persistence of intraepidermal spongiosis (asterisk), intraepidermal vesicles (arrowheads) and small, bright, inflammatory cells (arrow); (E) clinical clearing; (F) LC-OCT showing normal epidermal appearance.

Table I. Demographic data of the patients and results

Patient	Age (years)	Sex	Treatment	Location	Results			
					T1 (2 weeks)		T2 (4 weeks)	
					IGA	LC-OCT AD pattern	IGA	LC-OCT AD pattern
"Young" group								
1	15	M	Pimecrolimus	Left forearm	Clearing	Present	Clearing	Absent
			Moisturizer	Right forearm	No change	Present	No change	Present
2	8	M	Pimecrolimus	Right arm	Clearing	Present	Clearing	Absent
			Moisturizer	Left arm	No change	Present	Mild improvement	Present
3	5	F	Pimecrolimus	Right axilla	Marked improvement	Present	Clearing	Absent
			Moisturizer	Left axilla	Mild improvement	Present	Mild improvement	Present
4	7	F	Pimecrolimus	Right arm	Mild improvement	Present	Clearing	Absent
			Moisturizer	Left arm	Mild improvement	Present	No change	Present
5	12	F	Pimecrolimus	Right arm	Mild improvement	Present	Marked improvement	Present
			Moisturizer	Left arm	Mild improvement	Present	Mild improvement	Present
6	7	M	Pimecrolimus	Right leg	Mild improvement	Present	Clearing	Absent
			Moisturizer	Left leg	No change	Present	Worsening	Present
7	7	F	Pimecrolimus	Left hand	Mild improvement	Present	Marked improvement	Present
			Moisturizer	Right hand	No change	Present	Worsening	Present
8	10	F	Pimecrolimus	Left forearm	Clearing	Absent	Clearing	Absent
			Moisturizer	Right forearm	Mild improvement	Present	Mild improvement	Present
9	11	M	Pimecrolimus	Right arm	Marked improvement	Present	Clearing	Absent
			Moisturizer	Left arm	Mild improvement	Present	Mild improvement	Present
10	9	F	Pimecrolimus	Abdomen (right)	Clearing	Absent	Clearing	Absent
			Moisturizer	Abdomen (left)	No change	Present	No change	Present
"Elderly" group								
11	65	M	Pimecrolimus	Right leg	Clearing	Present	Clearing	Absent
			Moisturizer	Left leg	No change	Present	No change	Present
12	65	F	Pimecrolimus	Left hand	Clearing	Present	Clearing	Absent
			Moisturizer	Right hand	No change	Present	Mild improvement	Present
13	68	M	Pimecrolimus	Right leg	Clearing	Present	Clearing	Absent
			Moisturizer	Left leg	No change	Present	Mild improvement	Present
14	66	F	Pimecrolimus	Left thigh	Mild improvement	Present	Marked improvement	Present
			Moisturizer	Right thigh	Mild improvement	Present	Mild improvement	Present
15	71	M	Pimecrolimus	Right forearm	Mild improvement	Present	Clearing	Absent
			Moisturizer	Left forearm	Mild improvement	Present	Mild improvement	Present
16	72	M	Pimecrolimus	Right hand	No change	Present	Marked improvement	Present
			Moisturizer	Left hand	No change	Present	Worsening	Present
17	69	F	Pimecrolimus	Left leg	Clearing	Absent	Clearing	Absent
			Moisturizer	Right leg	Mild improvement	Present	No change	Present
18	68	M	Pimecrolimus	Right leg	Mild improvement	Present	Clearing	Absent
			Moisturizer	Left leg	Mild improvement	Present	No change	Present
19	74	F	Pimecrolimus	Right forearm	Marked improvement	Present	Marked improvement	Present
			Moisturizer	Left forearm	Mild improvement	Present	Mild improvement	Present
20	70	F	Pimecrolimus	Left leg	Marked improvement	Present	Clearing	Absent
			Moisturizer	Right leg	No change	Present	Worsening	Present

AD:atopic dermatitis; IGA:investigator global assessment; LC-OCT:Line-field confocal optical coherence tomography.

Our clinical results after 4 weeks of treatment of AD with pimecrolimus are in line with previous studies (2). Interestingly, after the first 2 weeks of treatment, LC-OCT was able to reveal persistence of some alterations in 5 lesions despite them being clinically rated as clear. This may indicate that subclinical AD features may persist after apparent clinical resolution, suggesting that treatment may be continued until complete imaging normalization is achieved. On the contrary, the moisturizer-treated control lesions did not show clinical improvement and consistently maintained the AD LC-OCT pattern, confirming that the improvement observed in the lesions treated with pimecrolimus was attributable to the active treatment rather than to spontaneous remission.

Our findings may have a molecular and immunological explanation. In a recent study on AD patients in clinical remission, multiple skin biopsies were taken from different areas. In those areas that relapsed in the following weeks, and that underwent a previous biopsy, molecular signals reminiscent of active AD were found, including epidermal barrier dysregulation, chemokine signalling, increased vascular permeability and T-cell activity and infiltration, along with signs indicative of the pre-relapse state such as EGFR signalling and macrophage phagocytosis (1). These features support our findings that subclinical inflammation may persist in atopic skin even after clinical resolution, thus foreseeing AD relapses (1).

In conclusion, our study demonstrates the added value of LC-OCT as an objective instrumental tool to monitor the response to treatment in AD, highlighting its ability to detect subclinical disease activity and to support treatment decisions beyond clinical evaluation alone.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

IRB approval status: The study was approved by the local ethics committee # 37749.

Conflict of interest: Raffaella Mantegazza is an employee of Global Medical Affairs, Viatris, Italy

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