

Proactive vs. reactive psoriasis therapy: a long-term evaluation with dermoscopic and confocal microscopy assessment

S. CACCIAPUOTI, A. RUGGIERO, L. GALLO, G. FABBROCINI

Federico II University Dermatological Clinic, Naples, Italy

Abstract. – **OBJECTIVE:** The PSO-LONG trial demonstrated that proactive management of psoriasis based on the regular application of the fixed-dose combination calcipotriol and betamethasone dipropionate (Cal/BD) foam twice a week for 52 weeks prolonged the time to first relapse and reduced the number of relapses, compared with the reactive management. Nevertheless, data about proactive management in clinical practice are still poor. This observational study compares the Cal/BD foam proactive management of psoriasis with the reactive scheme in consecutive patients with localized mild-to-moderate psoriasis. The degree of the skin atrophy was also assessed with dermoscopic and confocal microscopy analyses.

PATIENTS AND METHODS: This retrospective observational study was conducted at the Federico II University Dermatological Clinic of Naples in adult patients treated with the fixed-dose combination Cal/BD foam (Enstilar®, Leo Pharma, Ballerup, Denmark) according to either a proactive or a reactive scheme (on-demand treatment). The observation time was 52 weeks.

RESULTS: 149 patients were involved. The effectiveness of the proactive therapy was sustained by the significant reduction of the mean number of relapses ($p=0.004$) and by the significant increase of the median time to relapse ($p=0.014$) compared to the reactive regimen. Compared to the baseline values, significant improvements in the Psoriasis Area and Severity Index (PASI) score, Investigator Global Assessment (IGA) score, and Skindex-16 index were reported. Dermoscopy and confocal microscopy analyses showed the absence of cutaneous atrophy during the proactive treatment and improved the lesion's appearance.

CONCLUSIONS: The proactive regimen represents a valuable therapeutic novelty in treating mild-to-moderate psoriasis.

Key Words:

Betamethasone dipropionate, Calcipotriene, Enstilar, Fixed-dose, Foam, Long-term, Proactive, Relapse, Topical treatment.

Introduction

Psoriasis is a chronic inflammatory skin disease that causes red, itchy, scaly patches, most commonly on the knees, elbows, trunk, and scalp¹. Most patients present with a localized form of the disease of mild to moderate severity². In this case, the fixed-dose combination of vitamin D analogue (calcipotriol [Cal]) and corticosteroid (betamethasone dipropionate [BD]) is recommended as first-line topical therapy due to its high efficacy and its favorable administration scheme^{3,4}.

Psoriasis has a relapsing/remitting presentation. Indeed, subclinical inflammation may persist even once the skin lesions are fully resolved, eventually leading to disease flares^{4,5}. Consequently, in clinical practice, psoriasis management is usually based on a reactive approach initiated as soon as psoriasis relapses⁶.

However, the recently published PSO-LONG trial demonstrates that proactive management based on the regular application of the fixed-dose combination Cal/BD foam twice a week for 52 weeks prolonged the time to first relapse, increased time of disease remission, and reduced the number of relapses, compared with the reactive management^{7,8}. Nevertheless, despite these satisfactory results that lead to the indication of Cal/BD foam in the maintenance treatment⁹, data about proactive management in clinical practice, particularly compared to the reactive management of psoriasis, are still poor. The traditional parameters used to assess the effectiveness of the topical treatments are generally based on scores that vary depending on the observer. To overcome this limitation, in addition to the clinical evaluations, some authors proposed to perform skin biopsies before and after the treatment to evaluate and monitor any changes. To this aim, dermoscopy and confocal microscopy, traditionally used to study skin tumors, have been extended and validated for chronic inflammatory skin diseases, including psoriasis^{10,11}.

This observational study aimed to evaluate the effectiveness of the proactive management of psoriasis with the Cal/BD foam combination and compare this regimen with the reactive scheme in consecutive patients with localized mild-to-moderate psoriasis. In addition, within this study, the degree of skin atrophy was assessed with dermoscopic and confocal microscopy evaluations to compare the proactive regimen with the reactive treatment and compare the dermoscopic/confocal microscopy results with the clinical findings.

Patients and Methods

Study Design and Patients

This retrospective observational study was conducted at the Federico II University Dermatological Clinic of Naples. It involved psoriasis adult (≥ 18 years) patients in treatment with the fixed-dose combination Cal/BD foam (Enstilar[®], Leo Pharma, Ballerup, Denmark) according to either a proactive regimen (twice weekly for 52 weeks) or to a reactive scheme (on-demand treatment), in the period between 1 June 2020 and 1 July 2021. The observation time for each patient was 52 weeks.

The selection criteria for patients treated with the proactive management were a diagnosis of localized psoriasis of mild-to-moderate severity and the ability to provide written, signed and dated informed consent before starting any study-related activity. Patients were not eligible if they presented other forms of psoriasis (guttate, erythrodermal, pustular) or other skin diseases/infections that may interfere with the examination of psoriasis lesions. If patients were on other psoriasis treatments, including (but not limited to) topical or systemic corticosteroids, other topical medications (e.g., coal tar), oral or biologic medications for psoriasis and ultraviolet (UV) light therapy, the following washout periods were needed: 2 weeks for topical therapy, 2 weeks for phototherapy, 12 weeks for biological or targeted therapies, 4 weeks for other systemic therapies. Women who are pregnant, nursing, or of child-bearing potential who are unwilling to use appropriate methods of contraception and patients reluctant to limit exposure to UV light were also excluded. At the investigator's discretion, current medical conditions would put the patient at significant risk or a history of allergy to any product component was also considered exclusion criteria.

The same selection criteria were considered for patients treated with the reactive approach.

The study was conformed to Helsinki's Declaration and was approved by the Local Ethics Committee (protocol approval code: 4521). All participants provided written informed consent.

Study Measures

The primary objectives of this study were the evaluation of the effectiveness of Cal/BD foam used as a long-term, twice-weekly treatment (proactive management) and the comparison of this regimen with reactive management. To this aim, the number of relapses during the study period and the time to first relapse were evaluated in the proactive management group and compared between the two therapy regimens.

Secondary efficacy endpoints were Psoriasis Area and Severity Index (PASI) score, which was evaluated in both treatment groups at the baseline and after 4 and 52 weeks of treatment, and the percentage of patients who achieved and maintained treatment success at week 52, according to Investigator Global Assessment (IGA).

The improvement in quality of life (QoL) was investigated in both groups after 52 weeks of treatment using the Skindex-16 score, obtained through a self-administered questionnaire that assesses the QoL of patients in three domains: burden of symptoms, social functioning and emotional responses. Skindex-16 used in this study was a single-page version of the original Skindex 62-item-version¹².

As a secondary aim, the degree of skin atrophy of the lesions treated with the Cal/BD foam combination was evaluated with dermoscopy and confocal microscopy. For this analysis, the selected lesions were small and slightly hyperkeratotic of the upper limbs, lower limbs, and trunk; injuries to the face, scalp and genital regions were excluded. Dermoscopy and confocal microscopy were acquired from the lesion center before treatment and after 52 weeks of therapy.

Dermoscopic images were acquired with DermLite Foto II Pro-Canon 11 digital camera; confocal microscopy images were acquired with RCM Vivascope 3000 (Mavig, Munich, Germany).

Specific criteria described in the literature were considered for monitoring treatment as follows.

Dermoscopic evaluation: evaluation of the vascular pattern (dotted, globular) and the degree of silver scales' presence. The presence of scarring and structureless areas was also assessed to evaluate atrophy after treatment.

Confocal microscope evaluation: evaluation of the thickening of the stratum corneum, of parakeratosis, of the number of inflammatory cells in the epidermis, of the presence of dilated dermal papillae

and reduction of the thickness of the interpapillary space, and of the degree of dilation of the vessels within the papillae. Evaluation of the reduction in the thickness of the epidermis and the presence of collagen striae was assessed in the superficial dermis to determine the state of atrophy after treatment.

Statistical Analysis

Data were analyzed by descriptive statistics. Categorical variables were compared using the Chi-squared test or the Fisher exact test where appropriate. Where appropriate, continuous variables were compared using the *t*-test or the non-parametric Mann-Whitney U test.

Results

Patients

The study involved 149 patients, 75 (50.3%) were treated with the proactive approach, and 74 (49.7%) were treated with reactive management. The baseline characteristics of patients are summarized in Table I.

Number of Relapses and Time to First Relapse

During the study period, the mean (standard deviation, SD) number of relapses in patients treated

Table I. Baseline characteristics of patients (n=149).

Features	Proactive group (n=75)	Reactive group (n=74)
Age (years); mean±SD	47±6	49±5
Male; n (%)	37 (49)	38 (51)
PASI score; mean±SD	7.1±5.2	7.9±6.7
IGA score; mean±SD	1.8±0.9	1.7±0.8
Skindex-16 score; mean±SD	15.6±15.3	17.8±19.9

SD: standard deviation; PASI: Psoriasis Area and Severity Index; IGA: Investigator Global Assessment.

with the proactive management was equal to 2.4 (1.8) and was significantly reduced compared with the number of relapses reported by reactive group patients (3.3 [1.9]; $p=0.004$).

Among patients treated with the proactive regimen, 24 (32.0%) did not relapse. For the others, the median time to first relapse was 6 weeks (95% CI: 4-12 weeks).

Considering patients treated with reactive management, 16 patients (21.6%) did not relapse. The median time to first relapse was 2 weeks (95% CI: 1-3 weeks) among the remaining patients.

Comparing the two groups with the proactive management, the median time to relapse was significantly longer than with the reactive approach ($p=0.014$) (Figure 1).

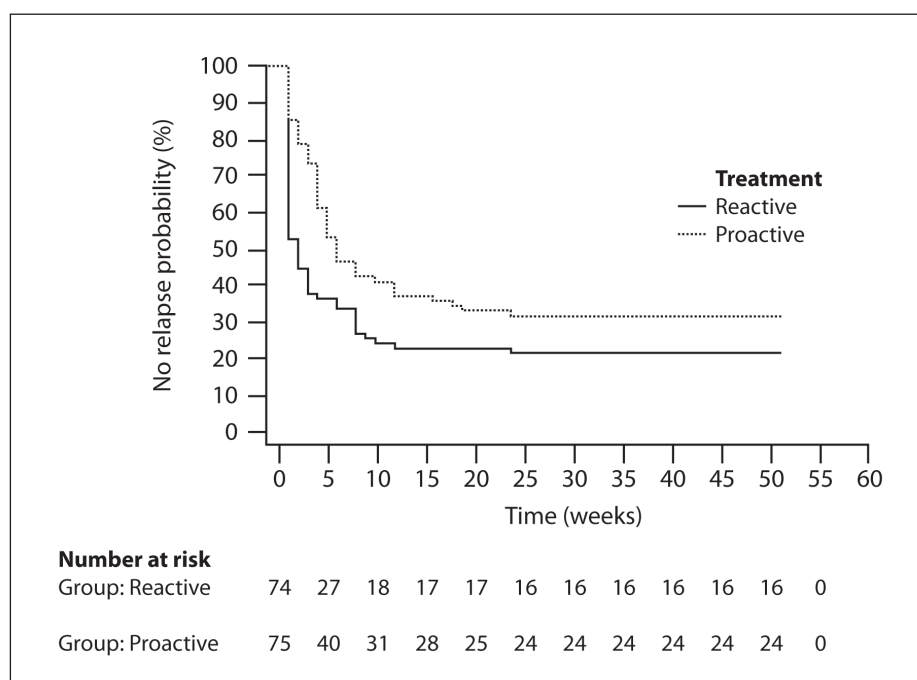


Figure 1. Time to first relapse during the proactive (green line, n=75) or reactive (orange line, n=74) management.

Table II. PASI score analysis.

	PASI score, mean (SD)		
	Baseline	Week 4	Week 52
Proactive management	7.1 (5.2)	4.7 (5.0)***	2.9 (4.6)***
Reactive management	7.3 (6.5)	4.8 (5.4)***	3.2 (4.6)***

*** $p < 0.001$. PASI: Investigator Global Assessment; SD: standard deviation.

PASI Score

Compared to the baseline evaluations, the mean PASI score significantly reduced after 4 and 52 weeks of treatment in patients treated with proactive management. The proportion of patients with PASI 90 and 100 was significantly higher after 52 weeks than after 4 weeks of treatment. The same trend was observed with the reactive regimen approach (Tables II and III). There was no significant difference in mean PASI score variation and the proportion of patients with PASI 75, 90 and 100 between groups.

IGA Score

The median IGA score showed a significant reduction after 52 weeks of treatment in both groups of patients ($p < 0.001$). There was no significant difference in median IGA score between groups.

Skindex-16 Score Evaluation

The mean Skindex-16 score was significantly reduced after 52 weeks of proactive treatment (mean [SD] = 10.2 [14.8]), if compared to the baseline value (mean [SD] = 15.6 [15.4]; $p < 0.001$). The same trend of reduction was observed after the reactive treatment (baseline: mean [SD] = 18.0 [19.8]; 52 weeks: 13.8 [16.7]; $p < 0.001$). There was no significant difference in the mean Skindex-16 score variation between groups.

Dermoscopic and Confocal Microscope Evaluations

A total of 20 lesions were analyzed, 10 for each treatment group. The lesions were in the trunk (11/20, 55%), in the lower limbs (4/20, 20%) and the upper limbs (5/20, 25%).

At baseline, the dermoscopic evaluation revealed a dotted vascular pattern over the entire area in most lesions (18/20; 90%), with a globular vascular pattern organized in clusters at the periphery (12/20; 60%) and the presence of superficial scales in all lesions (Figure 2).

The confocal microscopy analysis identified the hyperkeratosis and diffuse inflammatory infiltrate of the superficial layers in all the lesions analyzed, papillomatosis with consequent reduction of the interpapillary spaces on about 85% of each lesion and the presence of dilated vessels inside the papillae in more than 50% of all the lesions surface (Figure 3).

After 52 weeks of treatment, the dermoscopic analysis revealed in most patients the absence of the vascular pattern (proactive management: 8/10, 80%; reactive management: 7/10; 70%), the presence of the dotted pattern at the periphery of the lesion (proactive management: 2/10, 20%; reactive management: 3/10; 30%), and the absence of silver scales in all lesions. No structureless areas or areas of fibrosis were observed (Figure 2).

Table III. PASI 75, 90 and 100 by visit.

	PASI score, n (%)		
	PASI 75	PASI 90	PASI 100
Proactive management			
Week 4	54.0 (72.0)	6.0 (8.0)	6.0 (8.0)
Week 52	60.0 (80.0)	32.0 (42.7)***	27.0 (36.0)***
Reactive management			
Week 4	51.0 (68.9)	5.0 (6.8)	5.0 (6.8)
Week 52	64.0 (86.5)***	26.0 (35.1)***	24.0 (32.4)***

*** $p < 0.001$.

PASI: Investigator Global Assessment.

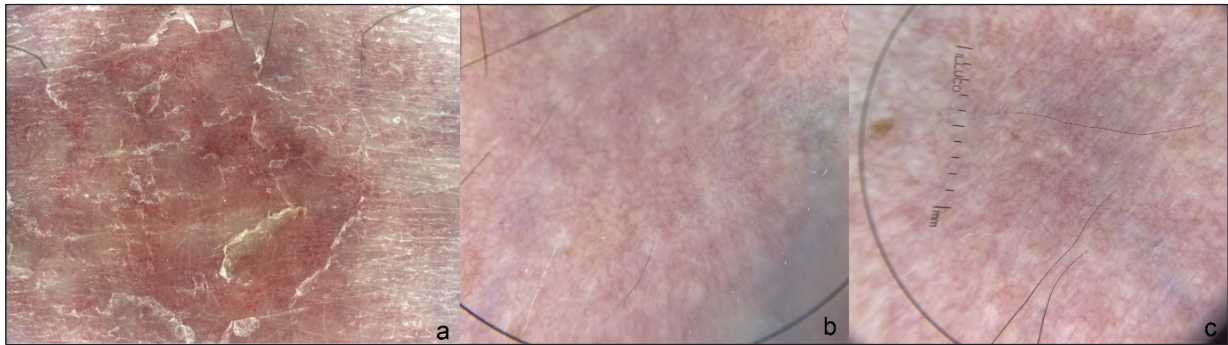


Figure 2. Dermoscopic images. **a**, Diffuse dotted vascular pattern, superficial desquamation at the baseline (original magnification, $\times 10$). **b**, Absence of desquamation and inflammation after 52 weeks in proactive treatment and absence of atrophy (original magnification, $\times 10$). **c**, Absence of desquamation and inflammation after 52 weeks of reactive treatment and absence of atrophy (original magnification, $\times 10$).

During confocal microscopy, a major reduction of hyperkeratosis and inflammatory infiltrate was observed in the superficial layers in most samples of both groups (proactive management: 9/10, 90%; reactive management: 8/10; 80%), reduction of papillomatosis and presence of a well-organized dermo-epidermal junction (8/10; 80%). Small areas of fibrosis in the superficial dermis were present only in one lesion for each group (Figure 3).

Discussion

The rationale for the long-term proactive management of psoriasis with topical therapy lies in the persistent subtle inflammation that characterizes psoriasis even during remission phases^{4,5}. In addition, the use of Cal/BD foam in the long-term proactive treatment of psoriasis is based upon the well-documented synergistic effect of the two components and the immunomodulatory properties shown by this compound¹³⁻¹⁵.

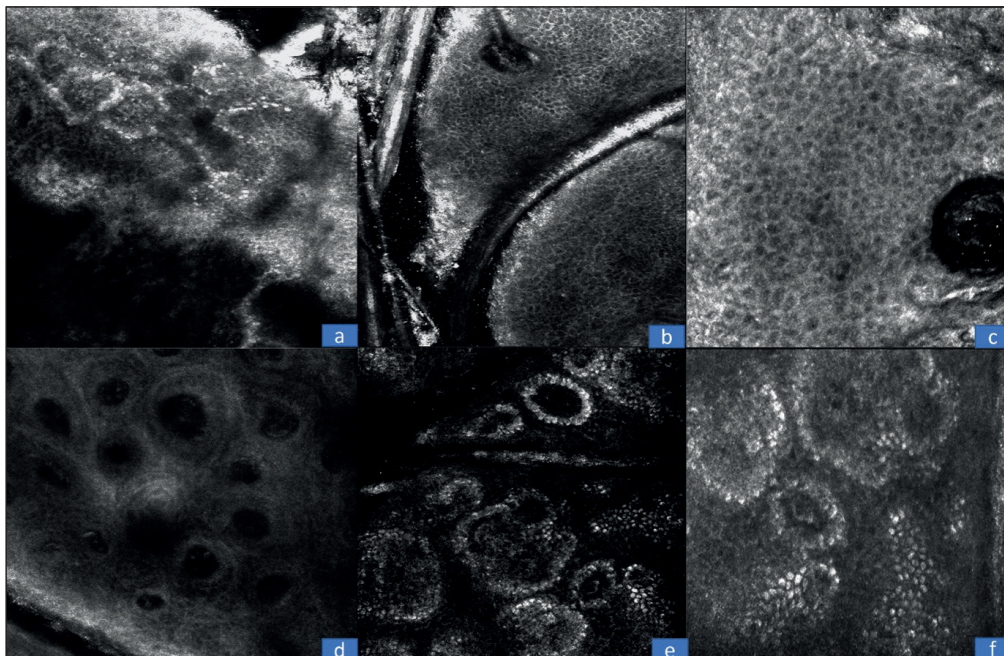


Figure 3. Confocal microscopy images (0.5x0.5 mm). **a**, Diffuse inflammatory infiltrates of the spinous layer in psoriatic lesion at baseline. **b**, Absence of inflammatory cells in the most superficial layers in a patient under proactive treatment after 52 weeks. **c**, Absence of inflammatory cells in the most superficial layers in a patient undergoing reactive treatment after 52 weeks. **d**, Papillomatosis at the dermal-epidermal junction level in psoriatic lesion at baseline. **e**, Normal dermal-epidermal junction after 52 weeks of proactive treatment. **f**, Normal dermal-epidermal junction after 52 weeks of reactive treatment.

The PSO-LONG study was the first and only phase III trial that evaluated the efficacy of the proactive long-term therapy with Cal/BD foam to treat mild-moderate psoriasis^{7,16}. Within this study, the regular application of Cal/BD with a proactive regimen in patients who achieved treatment success after a 4-week open-label phase was more effective if compared with the reactive management. The predicted number of relapses per year of exposure was reduced by one third with the proactive regimen (3.1 vs. 4.8 in the reactive group), prolonging the estimated median time to first relapse by 26 days and the proportion of days in remission for patients in this group of patients (estimated treatment difference: 11%, $p < 0.001$, corresponding to 41 extra days in remission over 1 year). These outcomes were paralleled by a favorable safety profile and a positive effect on the quality of life⁷.

New evidence on this topic, especially in clinical practice, is now required.

In this retrospective study conducted in a cohort of 149 consecutive patients with mild-to-moderate psoriasis, the effectiveness of the proactive long-term (52 weeks) therapy with the Cal/BD foam was sustained by the significant reduction of the mean number of relapses (2.4 vs. 3.3; $p = 0.004$) and by the significant increase of the median time to relapse (6 weeks vs. 2 weeks; $p = 0.014$), if compared to the traditional reactive regimen. In addition, significant improvements in the PASI score, IGA score, and Skindex-16 index during the study period were reported compared to the baseline values, further supporting the effectiveness and feasibility of the proactive long-term regimen in clinical practice and in agreement with literature data about the beneficial effect of the proactive approach on the patients' quality of life¹⁷.

Within this study, the dermoscopy and confocal microscopy analyses showed the absence of cutaneous atrophy during the proactive treatment of psoriasis and the improvement of the appearance of psoriatic lesions, in line with the clinical observations. According to the proactive regimen, these data support the use of the Cal/BD foam for the prolonged continuative period.

Conclusions

The results of this observational study support the effectiveness of the proactive regimen in the prevention of relapses, representing a valuable therapeutic novelty in the treatment of the mild-to-moderate forms of the disease, with an improvement of the quality of life for the patient.

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Conflicts of Interest

None of the Authors declared a conflict of interests.

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Authors' Contributions

Study conception and design: All; collection and interpretation of data: All; manuscript drafting: All; manuscript editing: All; approval to submit: All.

Ethics

This study was approved by the Local Ethics Committee (protocol approval code: 4521).

Informed Consent

Written informed consent was obtained from all individual participants included in the study.

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