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LONG-TERM TOPICAL MANAGEMENT OF PLAQUE PSORIASIS: A REVIEW OF THE DATA ON PROACTIVE MAINTENANCE WITH CAL/BD FOAM

Psoriasis is a common, chronic inflammatory condition that has a significant impact on quality of life (QoL)[1,2]. The goals of treatment focus on reduction of disease activity and improvement in QoL[3-6]. The UPLIFT survey of patients revealed that reduction of itch was the most important treatment goal followed by symptom control and skin clearance. Symptom improvement was the most important attribute of ideal therapy[7].

Short-term itch reduction and symptom improvement are attainable treatment goals with topical therapies, particularly for patients with mild-to-moderate disease[8]. Long-term psoriasis management can be challenging due to the recurrent and relapsing nature of the disease, loss of clinical response over time and poor treatment adherence[9]. In addition, steroid phobia[10] and strict adherence to the topical steroid labelling which limits their use to 4 consecutive weeks have been barriers to long-term topical steroid use. Published literature involving expert recommendations for the long-term topical management using a proactive treatment strategy to improve disease control and optimize patient adherence has recently emerged[9,11,12].

In atopic dermatitis, maintenance topical therapy with tacrolimus has been approved by regulatory agencies and supported by clinical practice guidelines[13,14]. This has not been the case in psoriasis management. This is partially due to the paucity of data demonstrating long-term efficacy and safety. A limited number of randomized controlled trials have investigated the use of topical corticosteroids (TCS) and vitamin D3 analogues or their combination utilizing various long-term approaches including continuous therapy, intermittent therapy, step-down approach, sequential or pulse regimens and proactive maintenance therapy[12].

Continuous topical long-term therapy on any area with psoriasis was investigated using clobetasol propionate 0.05% ointment (clobetasol propionate 0.05% ointment vs betamethasone valerate 0.1% ointment vs fluocinolone acetonide 0.025% twice daily for 6 months)[15,16], tacalcitol 4ug/g (once daily for 3-18 months)[17,18,19], calcitriol 3ug/g (twice daily for up to 78 weeks)[20], demonstrating overall safety and maintenance of disease control.

Calcipotriol 50ug/g plus betamethasone dipropionate 0.5mg/g (Cal/BD) gel and foam were studied as long-term chronic intermittent therapy for scalp psoriasis and psoriasis of the trunk and limbs. Cal/BD gel was applied once daily until clearing, followed by reactive treatment for up to 52 weeks on the scalp and Cal/BD

foam was applied on areas outside the scalp once daily until clearing, followed by reactive treatment for 6 months. Both trials demonstrated maintenance of disease control, improved adherence and no safety concerns[21,22].

The step-down treatment approach includes an induction schedule followed by a maintenance schedule. Step-down therapy for scalp psoriasis was investigated in 2 studies using clobetasol propionate 0.05% shampoo (once daily x 4 weeks followed by twice weekly for 6 months)[23] and Cal/BD gel (once daily until remission then twice weekly for 12 weeks)[24]. Cal/BD ointment (once or twice weekly for 3 months as a maintenance in patients with stable disease)[25] and Cal/BD gel (once daily for 8 weeks then twice weekly on weekends for 8 weeks)[26] were used in step-down approach for trunk and limb psoriasis. These studies reported maintenance of disease control, no long-term safety concerns and an optimized patient experience.

Sequential therapy has been reported with TCS and non-steroidal topical agents with weekday/weekend treatments. Lebwohl *et al*. (1998) reported on the use of calcipotriene ointment twice daily on weekdays and halobetasol ointment twice daily on the weekends for 6 months[27]. In addition to maintenance of disease control and safety, the authors reported that this schedule increased the interval for recurrence. Koo *et al*. (2006) utilized clobetasol propionate 0.05% foam and calcipotriene 0.005% ointment twice daily in combination or as monotherapy for 2 weeks followed by calcipotriene ointment once daily on weekdays and clobetasol foam or vehicle once daily on weekends for 24 weeks and reported maintenance of disease control and optimized patient experience[28]. Similar long-term outcomes were observed by Kragballe *et al*. (2006) in patients using Cal/BD ointment once daily PRN for 52 weeks continuously or alternating between 4-week periods with calcipotriol ointment or 4-week Cal/BD ointment followed by 48 weeks of calcipotriol ointment[29,30].

A topical fixed combination Cal/BD foam demonstrated efficacy and favorable safety in Phase II and III clinical trials[31-34]. Fifty-three percent of patients achieved treatment success with the Cal/BD foam at week 4 compared to 4.8% of patients in the foam vehicle arm[32]. Pooled analyses of the three Phase II/III studies revealed early improvements in modified Psoriasis Area Severity Index (PASI) and QoL, as early as week 1, and rapid reduction in itch as early as day 3 through 4 weeks of therapy that were associated with significant improvements in itch-related sleep loss and sleep QoL[35,36]. Cal/BD foam has also shown superior efficacy to its individual components, calcipotriol and betamethasone dipropionate, Cal/BD gel and ointment[31,33,34]. Cal/BD foam demonstrated greater health related QoL improvement in patients with psoriasis than Cal/BD gel over 12 weeks of treatment[37].

PSO-LONG, the first randomized controlled trial to investigate proactive psoriasis maintenance therapy, was a phase III multicenter trial that included a 4-week open-label, lead-in phase and a 52-week, randomized, double-blind, vehicle-controlled maintenance phase (**Figure 1**). It enrolled 650 patients from the United States, Canada, United Kingdom, France, Poland, and Germany with truncal psoriasis, limb psoriasis, or both, involving 2-30% of body surface area (BSA), physician global assessment of disease severity (PGA) score of mild or higher (≥2) and modified PASI (mPASI) score ≥2 at baseline of the open-label lead-in phase[38].

The primary objective of the trial was to compare the efficacy of Cal/BD foam twice weekly for proactive management with vehicle foam (reactive management). The clinical trial endpoints and outcomes are outlined in **Table 1**.

During the open-label, lead-in phase patients were instructed to apply Cal/BD foam once daily for 4 weeks. Patients who achieved treatment success (PGA score of clear or almost clear with ≥2 grade improvement from baseline) entered into the maintenance phase and were randomized 1:1 to receive either Cal/BD foam (proactive management arm) or vehicle foam (reactive management arm) twice-weekly (2-3 days apart on fixed days) for 52 weeks on psoriatic plaques that cleared or almost cleared during the lead-in phase or after treatment relapse (PGA score mild or higher). Psoriasis relapse was assessed at scheduled visits every 4 weeks and unscheduled visits initiated by the patient. Upon relapse, regardless of the treatment arm, patients received Cal/BD foam rescue treatment, applied once-daily for 4 weeks. Maintenance treatment was resumed if PGA clear or almost clear was regained. If PGA clear or almost clear was not achieved, the patients were discontinued from the trial. Disease rebound was defined as mPASI≥12 and an increase in mPASI≥125% of the baseline mPASI value, or new pustular, erythrodermic psoriasis within 2 months of treatment discontinuation in the open-label lead-in phase, after discontinuation of recue treatment, or after the end of the maintenance phase. This was assessed during the 8-week safety follow up period after the end of the study/early withdrawal.

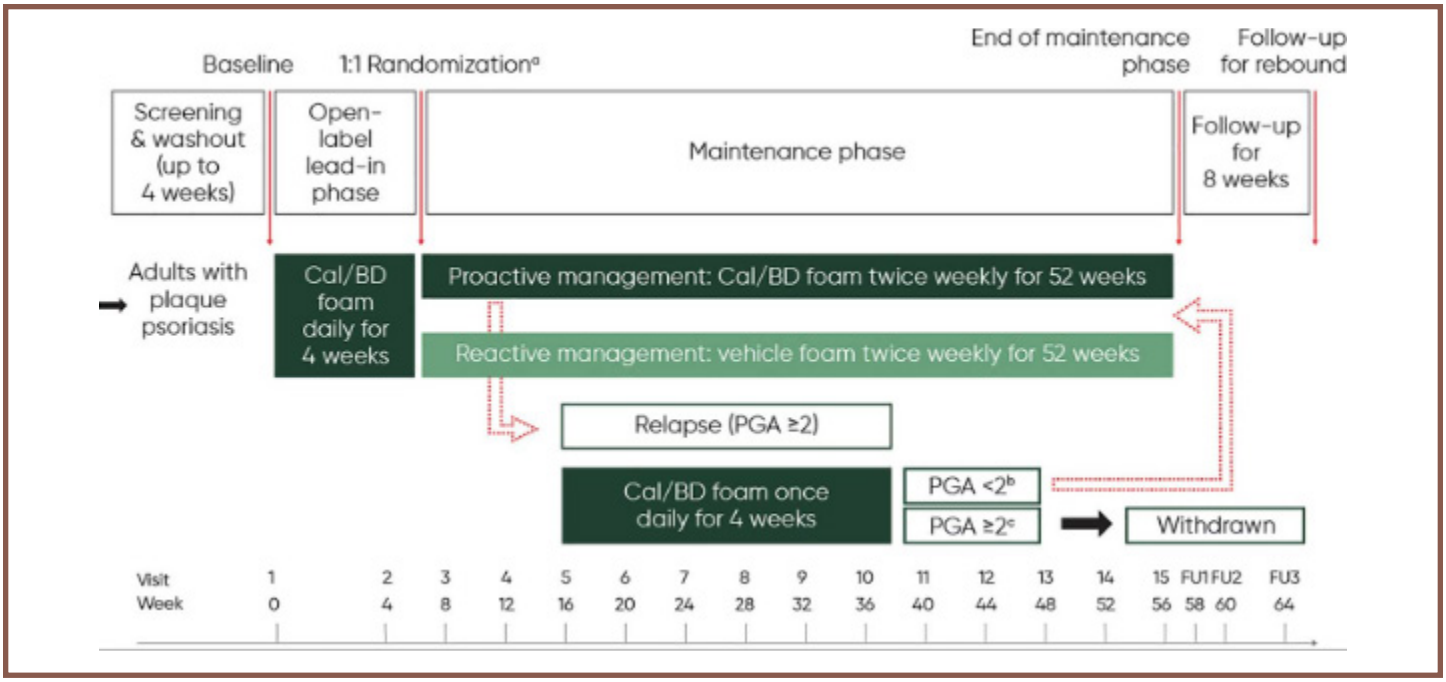

Figure 1: PSO LONG trial design. [a]Patients with treatment success at end of open-label lead-in phase (PGA score 'clear'/'almost clear' [PGA < 2] with ≥ 2-grade improvement from baseline) were randomized 1:1 in the maintenance phase. [b]Following 4 weeks of once-daily rescue treatment, patients who regained PGA < 2 ('clear'/'almost clear') re-started the twice-weekly maintenance treatment according to the original randomization scheme. cPatients who did not regain a PGA score < 2 ('clear'/'almost clear') following 4 weeks of once-daily rescue treatment were withdrawn from the trial. *Cal/BD* calcipotriene 0.005%/betamethasone dipropionate 0.064%, *FU* follow-up, *PGA* Physician Global Assessment. Adapted from *J Am Acad Dermatol*. 2021;84

Clinical trial endpoints		Proactive group	Reactive group
Primary	Time to first relapse (PGA score mild or higher)	56 days	30 days
Secondary	Proportion of days in remission (PGA score clear or almost clear)	41 extra days in the proactive group compared to the reactive group	
Secondary	Number of relapses per year of exposure	3.1days	4.8 days
Exploratory	Number of active treatment days	37.5 additional active treatment days per year in the proactive group compared to the reactive group	

Table 1. PSO-LONG clinical trial endpoints and outcomes[38]

Eighty-five percent of patients enrolled in PSO-LONG had moderate disease and 6.5% of patients had severe psoriasis. Eighty percent of patients (n=521) achieved treatment success after the initial open-label period and were re-randomized to the proactive (n=256) and reactive (n=265) management arms. Forty-six percent of patients (n=251) completed the 52-week maintenance phase[38].

During the maintenance phase, the estimated median time to first relapse was prolonged by 26 days for patients in the proactive group (56 days for proactive arm and 30 days for reactive arm) (**Figure 2**). The risk of experiencing the first relapse was reduced by 43% in the proactive versus the reactive arm (hazard ratio, 0.57; 95% CI, 0.47-0.69; P<0.001). Thirty patients in the proactive arm and 6 patients in the reactive arm did not experience relapse during the 52 week maintenance phase. In addition, over 52 weeks, patients in the proactive arm had 41 more days in remission and a reduced number of relapses compared to the reactive arm (3.1 versus 4.8 relapses per year of exposure). On average, the proactive group had 37.5 additional active treatment days per year versus the reactive group. Patients with more severe disease at baseline showed greater benefit with the proactive management compared to patients with milder disease[39].

Due to randomization errors, 545 patients were included in the safety analysis set. There were no new safety concerns reported during the maintenance phase. Overall, the incidence of all adverse events (AEs) was similar between treatment arms (303 events in

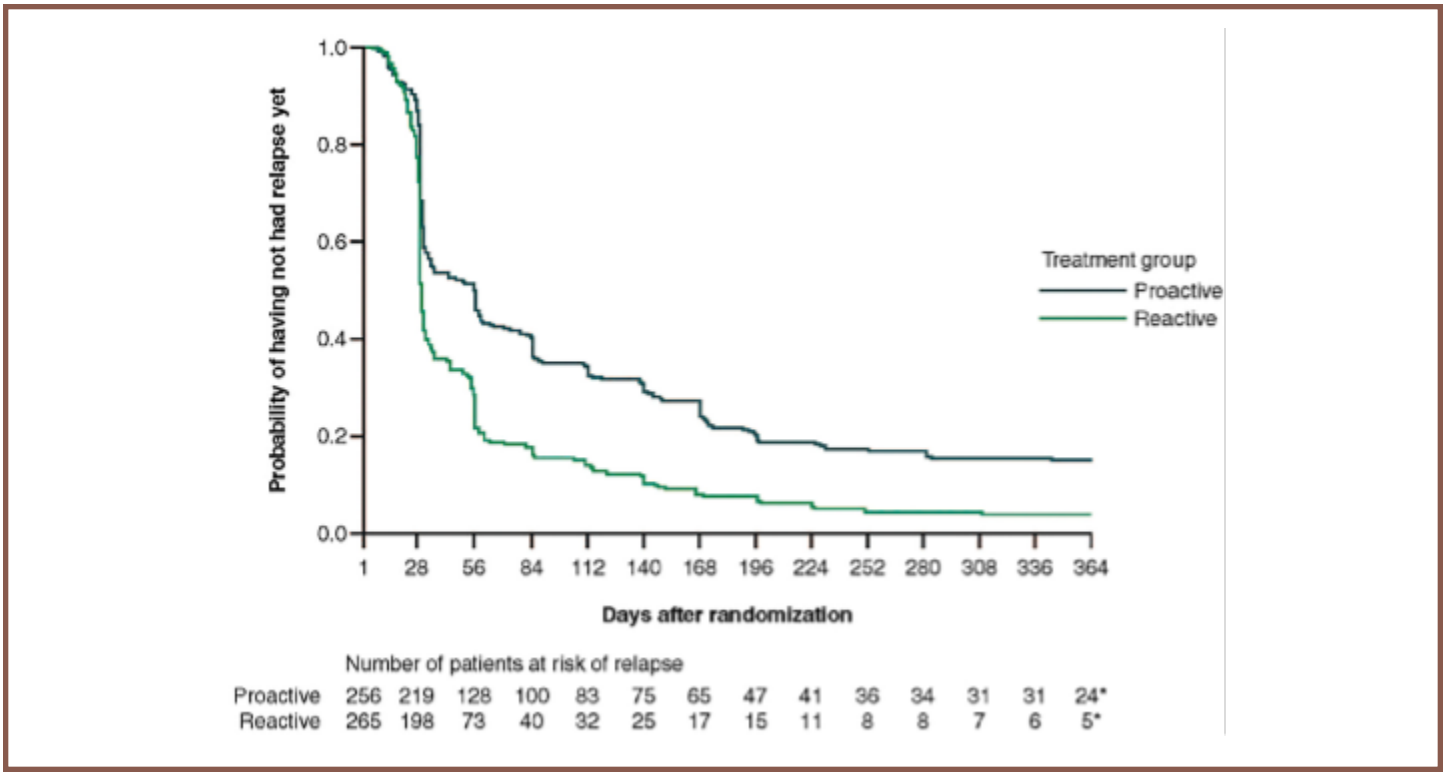

Figure 2: Time to first relapse during the maintenance phase with proactive management or reactive management. Note: patients who did not achieve physician's global assessment <2 after 4 weeks of once-daily rescue treatment following relapse were withdrawn from the trial but are included within this Kaplan–Meier curve. *30 patients in the proactive group vs. 6 patients in the reactive group finished the trial without experiencing first relapse but had their final visit prior to Day 364. Adapted from *J Am Acad Dermatol.* 2021;84

133 patients (48.9%) in the proactive group vs 279 events in 130 patients (47.6%) in the reactive group). The most frequently reported AEs (≥5% of subjects) were nasopharyngitis and upper respiratory tract infection, which were assessed as not related to the use of trial product[38].

In the proactive group, 5 (1.8%) subjects experienced 5 treatment-emergent adverse events (TEAEs) judged to be related to product use, versus 8 TEAEs in 7 (2.6%) patients in the reactive group. None of the TEAEs were serious and no serious AEs were judged to be related to the treatment[38]. There were 2 events that led to withdrawal in 2 subjects in the proactive group and 1 event in the reactive group[38].

Importantly, no patients in either group experienced skin atrophy at any point during the trial. The treatment was well tolerated with no significant differences between proactive and reactive groups[40]. The number of rebounds was not increased in the proactive group, as demonstrated in **Table 2**. Most patients were within the normal range for both serum and urine calcium which remained stable over time[38].

A subgroup of patients (n=66) with BSA 10-30% and PGA moderate or higher (PGA ≥3) underwent hypothalamic pituitary adrenal (HPA)-axis testing at baseline, randomization, at 28 weeks, and at the end of the maintenance phase/early withdrawal (52 weeks). No clinically relevant effect on the HPA-axis by sub-group analysis was observed and there were no new safety signals. Four patients (2, proactive; 2, reactive) had a serum cortisol concentration </=18ug/dL 30 minutes after adrenocorticotropic hormone challenge, and one patient in the proactive group had a serum cortisol concentration </=18ug/dL 60 minutes after the adrenocorticotropic hormone challenge. No patients had a serum concentration </=18 ug/dL at both time points[38]. Similar to the full analysis data set population, patients in the HPA-axis subgroup using proactive regimen had experienced longer median time to first relapse (111 versus 31 days), reduced risk of first relapse (hazard ratio: 0.49; p = .029), greater proportion of days in remission (17%; p = .001) and reduced rate of relapse (60% reduction; p < .001) compared to the reactive regimen[41].

Significant improvements in QoL and patient-perceived symptoms were seen in post-hoc PSO-LONG sub-analysis[42]. This sub-analysis revealed that patients in the proactive group had a significantly better Dermatology Life Quality Index (DLQI) (2.95 vs 3.4, difference -0.45, P= 0.007), psoriasis symptom inventory (PSI) scores (4.99 vs 5.74, difference -0.75, P=0.0128) and numerically better scores on the EuroQoL five dimensional questionnaire (EQ-5D-5L-PSO) (0.89 vs 0.88, difference 0.01, P=0.0842) versus

Rebounds	Proactive group (n=272)	Reactive group (n=273)
After open-label phase	6	7
After a relapse	4	17
In the maintenance phase	0	1

Table 2. Patients who experienced rebounds during PSO-LONG trial[38]

patients in the reactive group. In addition, baseline flare was associated with worse patient reported outcomes (PROs) than at the start of relapse. Patients with relapse had worse PROs than patients in remission suggesting that disease relapses may have a significant impact on QoL[42].

Another post-hoc analysis examining the impact of psoriasis on work and activity revealed that using Cal/BD foam daily for 4 weeks significantly improved psoriasis-related work presenteeism and reduced total work productivity impairment (TWPI) and total activity impairment (TAI) over 56 weeks, with significant improvements observed as early as 4 weeks after the baseline visit[43]. The proportion of patients who reported that their psoriasis prevented them from working or studying showed a relative change of 62.5% from baseline to week 4 ($P < 0.0003$), 69.2% from baseline to week 28 ($P < 0.0126$), and 22.2% from baseline to week 56 ($P=0.4795$). The proportion of patients reporting an impact on work productivity (as measured by presenteeism and TWPI) and activity impairment (as measured by both DLQI-question7b and TAI) also decreased. Improvements in presenteeism, as opposed to absenteeism, appeared to drive the majority of indirect TWPI-related cost savings[43]. The data sub-analysis focusing on a Finnish cohort revealed a markedly lower cost-per-responder when examining mPASI75, mPASI≤2, and DLQI≤1 responses in proactive vs reactive groups[44]. The last endpoint did not demonstrate statistical significance, which was likely impacted by the small number of patients left in the study.

The findings of the PSO-LONG trial demonstrate benefits of a proactive approach, providing patients and clinicians with a therapeutic algorithm to optimize disease control and reduce the number of relapses without compromising safety. The proactive approach may be of particular benefit for patients with seasonal flares, for those who experience frequent disease relapses or relapses upon holding of the topical treatment, for patients who have completed phototherapy to maintain treatment benefit, for patients who have difficulty accessing healthcare and for patients with moderate-to-severe disease who are reluctant to pursue systemic therapy.

PSO-LONG provides additional reassurance about the safety of Cal/BD foam when using the proactive management approach on clear or almost clear skin over 52 weeks with no signal for disease rebounds, skin atrophy, laboratory abnormalities or HPA-axis suppression, even in patients with higher disease burden.

A proactive approach to topical psoriasis management may be particularly relevant during the COVID-19 pandemic or at times where patients may encounter difficulties accessing healthcare, allowing patients to exercise proactive disease control.

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