Wiley
Dermatologic Therapy
Volume 2024, Article ID 2351576, 14 pages
https://doi.org/10.1155/2024/2351576

WILEY

Review Article

The Importance of the Formulation in the Treatment of Psoriasis: The Case of Calcipotriol/Betamethasone

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Received 22 March 2023; Revised 4 October 2023; Accepted 27 June 2024

Academic Editor: Xiaoming Liu

Psoriasis is a prevalent chronic inflammatory skin disease impacting 1 to 3% of the general population in the Western World. Topical therapies are the most often used treatment in psoriasis, frequently as ancillary treatments to traditional systemic or biologic treatments in individuals with severe disease. Topical therapy with fixed-dose combination of a vitamin D analogue (calcipotriol (Cal)) and corticosteroid (betamethasone dipropionate (BD)) has been recommended as first-line topical treatment, and its efficacy and safety are supported by an increasing body of evidence. Ointment, gel, cream, and foam are the four distinct formulations of fixed-dose Cal/BD combination that have been authorized for the treatment of psoriasis. Several studies have compared these formulations in terms of efficacy, safety, and patients' satisfaction. The objective of this study is to review all the comparative studies performed in patients with psoriasis of the Cal/BD foam formulation with respect to other topical treatments containing Cal and BD, either individually or in combination. The results of the studies published on this topic have shown that Cal/BD foam is more efficacious than both individual Cal/BD and Cal/BD ointment, gel, and cream. The safety profile, QoL, patient satisfaction, and cost-effectiveness were also higher for the Cal/BD foam formulation in different studies. Although more real-world clinical experience is required to validate the available data, Cal/BD foam may be the treatment of choice for both flare management and proactive maintenance treatment of psoriasis.

1. Introduction

Psoriasis is a prevalent chronic inflammatory skin disease impacting 1 to 3% of the general population in Western countries [1]. Patients with psoriasis display a wide range of clinical phenotypes, the most common being, plaque psoriasis (80–90% of cases) [1]. Mild forms of psoriasis, defined by less than 3–5% of the body surface area (BSA) involvement, account for the vast majority of patients (75%) and can be managed with topical treatment [2]. As a result, topical therapies are the most used treatment in psoriasis, either alone or in combination with systemic (small molecule or biologic) treatments in patients with severe disease (>10% BSA) [3]. The success of a topical therapy in psoriasis is determined by different variables, including skin type, plaque thickness, and, most importantly, patient adherence [4], which is especially low in this disease [5, 6]. Cal/BD topical formulations are usually recommended and employed as first-line topical therapy for psoriasis because of its effectiveness an convenience of once-daily application.

Four distinct formulations of fixed-dose Cal/BD combination—ointment, gel, cream, and foam—are approved for treating mild-to-moderate psoriasis, demonstrating consistent efficacy and safety [7, 8]. Several studies have compared the various Cal/BD formulations in terms of effectiveness, safety, and patients' satisfaction [9–16]. A review performed by Megna et al. studied the efficacy of different Cal/BD formulations for the treatment of psoriasis

and concluded that Cal/BD foam was superior to both gel and ointment formulations in mild-to-moderate psoriasis treatment [17]. A potential reason for this is the formation of a stable, supersaturated solution of the active ingredients upon the application of Cal/BD foam. This results in minimal crystallization and increased skin penetration, thereby increasing the bioavailability of Cal and BD. The Cal and BD concentrations are altered when expelled from the can, transforming from a pressurized liquid state to a foam state (Figure 1) [18–20].

The objective of this review is to provide an updated narrative of the comparative studies performed in patients with psoriasis of the Cal/BD foam formulation with respect to other topical treatments containing Cal and BD, either individually or in combination. The review draws from the most recent studies on this topic, compiled in Table 1 (clinical trials) and Table 2 (other studies), aiming to update previous reviews on the subject.

2. Cal/BD Foam versus Either Active Principle Alone

Several studies, including clinical trials and meta-analyses, have compared the combination of Cal/BD with its individual components. A single-center, investigator-blinded experiment that involved 24 patients with plaque psoriasis was the first published clinical trial to evaluate Cal/BD foam versus (vs.) BD alone in a four-arm study (Cal/BD foam, Cal/BD ointment, BD foam, and foam vehicle). This research included intraindividual comparisons performed through a version of the psoriatic plaque test created by Dumas and Scholtz [9, 34]. At week 4, the total clinical score (TCS; sum of erythema, scaling, and lesional thickness) dropped significantly on test locations treated with Cal/BD foam (-6.00 ± 1.27), when compared to the sites treated with Cal/BD ointment (-5.25 ± 1.78; $p = 0.038$), BD foam (-4.96 ± 1.85; $p = 0.005$), or foam vehicle (-1.88 ± 1.12; $p < 0.001$) [9]

In the fourth week of the study Cal/BD foam treatment had a significantly greater effect on reducing TCS (total clinical score) compared to Cal/BD ointment, BD foam, and foam vehicle. Specifically, Cal/BD foam reduced TCS by an average of -6.00 ± 1.27, which was −0.75 lower than Cal/BD ointment (95% CI −1.46 to −0.04, p value = 0.038). Furthermore, Cal/BD foam showed a greater effect on reducing TCS than BD foam and foam vehicle, with differences of −1.04 and −4.13, respectively (95% CI of −1.75 to −0.33 for BD foam and −4.83 to −3.42 for foam vehicle, with p values = 0.005 and <0.001, respectively)

A larger (302 patients) clinical trial comparing Cal/BD, Cal, and BD treatments was published in 2016 [21]. At Week 4, 45% of the individuals treated with Cal/BD foam attained therapeutic success; this rate was significantly higher than those achieved with Cal foam (14.9%; $p < 0.001$) or BD foam (30.7%; $p = 0.047$). Regarding the scalp, 53% of the patients reached treatment success using the Cal/BD foam, a greater percentage than in those treated with Cal foam (35.6%; $p = 0.021$), but not statistically significant when compared to the BD foam group (47.5%; $p = 0.45$) [21]. Also, mean psoriasis area and severity index (PASI) score for body psoriasis significantly improved in the three arms of this study by week 4, from a population baseline score of 7.6 to 2.7 with Cal/BD aerosol foam, 4.39 with Cal aerosol foam (mean difference −2.03; $p < 0.001$) and 3.37 with BD aerosol foam alone (mean difference −1.19; $p < 0.001$) [21].

In 2016, a pooled meta-analysis and literature review including psoriasis patients treated with Cal/BD aerosol foam ($n = 564$), BD aerosol foam ($n = 101$) and Cal aerosol foam ($n = 101$) was published [27]. The authors concluded that the treatment with the Cal/BD aerosol foam formulation showed significant higher effectiveness in treating psoriasis vulgaris compared to the individual active components, resulting in more extensive and rapid decrease in disease severity and itching alleviation [27]. Specifically, therapeutic success at week 4 was reached by 51% of patients treated with Cal/BD aerosol foam, compared to 31% and 15% achieved with BD aerosol foam and Cal aerosol foam, respectively [27]. Furthermore, mean decreases in modified PASI (mPASI) were higher with Cal/BD aerosol foam (72%) than with BD aerosol foam (53%) or Cal aerosol foam (43%). The same trend occurred with PASI75 (75% or greater reduction in PASI with respect to baseline) response rates: 51% for Cal/BD aerosol foam, 34% for BD aerosol foam, and 18% for Cal aerosol foam [27].

In summary, the available data indicate a greater efficacy of the Cal/BD foam combination vs. individual Cal and BD components administered using the foam formula.

3. Cal/BD Foam versus Other Formulations

3.1. Foam versus Ointment. Different head-to-head studies comparing the outcomes on psoriasis patients of Cal/BD foam vs. ointment include clinical trials and a cost-utility analysis.

In study carried out by Queille-Roussel et al. [9], the mean TCS was significantly lower on test sites treated with Cal/BD foam (-6.00 ± 1.27) compared with Cal/BD ointment at week 4 (-5.25 ± 1.78; $p = 0.038$) [9]. Total skin thickness was also reduced in Cal/BD foam-treated areas when compared to Cal/BD ointment [9].

Another double-blind multicenter phase II study, comparing the effectiveness and safety of foam vs. ointment version of Cal/BD compound, included a total of 376 patients during a total 4-week period treatment [10]. Changes in modified psoriasis area and severity index (mPASI; excluding the head, which was not treated) values were significantly greater for foam when compared to the ointment version at week 1 (mean difference −0.7; $p = 0.001$) and week 4 (mean difference −0.6; $p = 0.005$). Complete or almost complete regression of psoriasis lesions was achieved in a higher percentage of patients in the foam-treated group than in the ointment group (54.6% vs. 43.0%; $p = 0.025$) [10]. The authors of the study concluded that foam Cal/BD was more effective and safer than the ointment Cal/BD formulation [10].

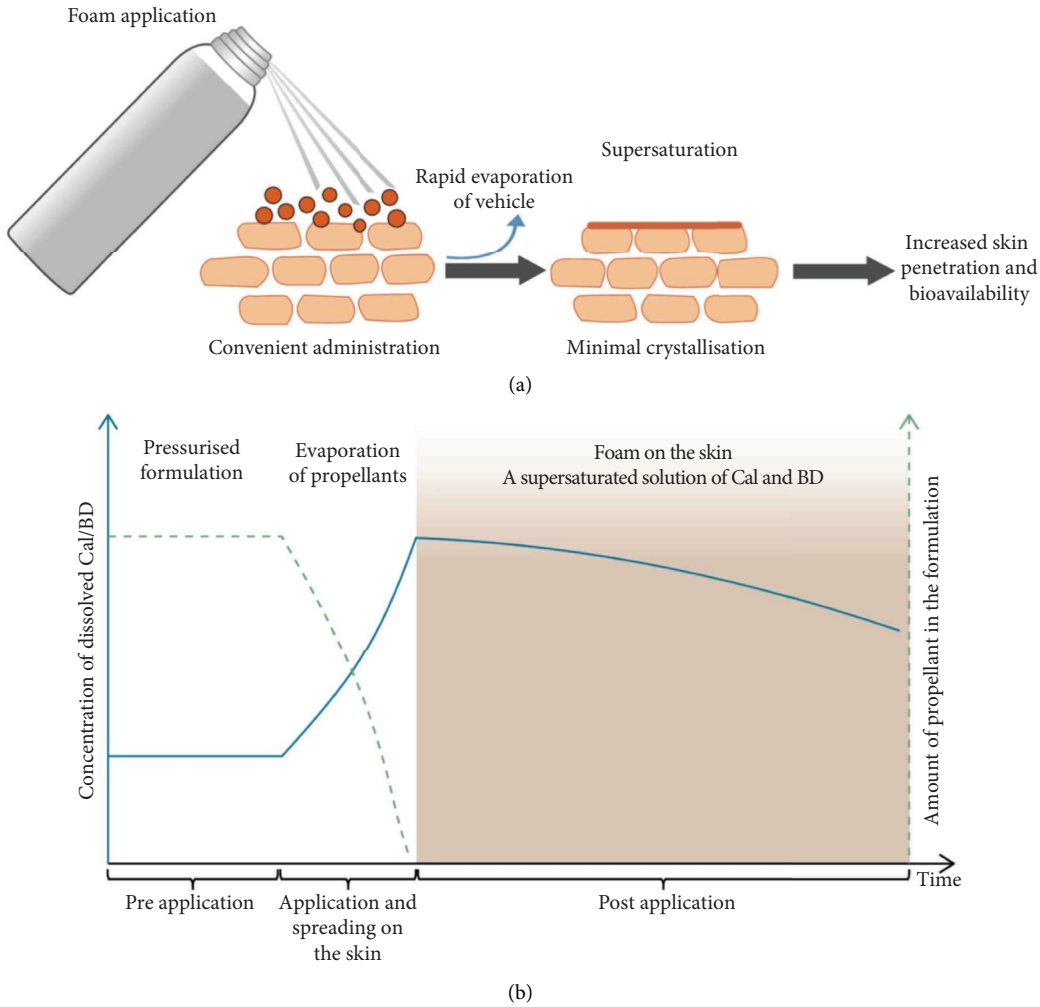

FIGURE 1: (a) Formulation of a supersaturated formulation on the skin following application of Cal/BD foam originally published in Gennari et al. [14] reproduced with kind permission from Eureka Science (FZC) and Bentham Science Publishers, Ltd. (b) Change in concentration of active ingredients dissolved in Cal/BD foam formulation over application time originally published in Lind et al. [15] reproduced with kind permission from Springer Full figure originally published in Teda et al. [16] reproduced with kind permission from Wiley. BD, betamethasone dipropionate (0.5 mg/g); Ca, calcipotriol (50 μg/g).

Cost-effectiveness is one of the criteria used to select the best option within the existing therapeutic arsenal [35]. A cost-utility analysis comparing Cal/BD foam to ointment for the topical treatment of psoriasis was carried out in Sweden [11]. The study revealed that the foam formulation was more expensive than the ointment. However, the foam formulation was more effective, because patients required fewer consultations and had a reduced likelihood of advancing to phototherapy/methotrexate treatment than patients treated with the ointment formulation [11]. Finally, the authors concluded that the Cal/BD foam formulation was projected to be more cost-effective than the ointment version in managing psoriasis vulgaris.

In summary, the current body of evidence indicates greater effectiveness and cost-effectiveness of the Cal/BD foam version than the Cal/BD ointment for the treatment of psoriasis.

3.2. Foam versus Gel. Two clinical trials have compared Cal/BD foam and gel formulations. PSO-ABLE evaluated both efficacy and QoL, and PSO-INSIGHTFUL measured patient preference with respect to these two Cal/BD vehicles.

A total of 463 patients participated in the PSO-ABLE phase III clinical trial [12]. After 4 weeks of treatment, Cal/BD foam was significantly more efficacious than treatment with the gel formulation for 8 weeks, with similar tolerability [12]. Cal/BD foam also attained superior treatment success rates (38% vs. 22%; $p < 0.001$) and mPASI75 response rates (52% vs. 35%; $p < 0.001$) compared to Cal/BD gel [12]. Adverse drug reactions were documented in 7.6% of Cal/BD foam individuals vs. 3.7% in the Cal/BD gel treatment group [12]. All were single events, except for five cases (2.7%) where patients experienced itchiness after using Cal/BD aerosol foam, and three cases (1.6%) where psoriasis worsened after using Cal/BD gel [12]. There were no

Table 1: Summary of findings of clinical trials comparing Cal/BD formulations.

Cal/BD foam versus either component alone							
Authors	Reference	Study	Number of subjects	Treatments	Treatment duration	Study type	Main findings
Queille-Roussel et al.	[9]	NCT01347255	24	Cal/BD foam, BD foam	4 weeks	Phase IIa clinical trial	(i) Cal/BD foam significantly decreases TCS *versus* BD foam ($p = 0.005$)
Lebwohl et al.	[21]	NCT01536938 (LEO90100–7)	302	Cal/BD foam, Cal foam, BD foam	4 weeks	Phase II clinical trial	(i) Significantly more Cal/BD foam treated patients achieved more treatment success rates than Cal foam ($p < 0.001$) or BD foam ($p = 0.047$) (ii) Significantly more Cal/BD foam treated patients achieved more scalp treatment success rates than Cal foam ($p = 0.021$) but when compared to BD foam ($p = 0.45$) (iii) Significantly more Cal/BD foam treated patients achieved a PASI score improvement when compared to Cal foam ($p < 0.001$) or BD foam ($p < 0.001$)
Cal/BD foam vs other formulations Foam vs ointment							
Authors	Reference	Study	Number of subjects	Treatment duration		Characteristics of the study	Main findings
Queille-Roussel et al.	[9]	NCT01347255	24	4 weeks		Phase IIa clinical trial	(i) Mean TCS was significantly lower on test sites treated with Cal/BD foam compared with Cal/BD ointment ($p = 0.038$) (ii) Total skin thickness was reduced in Cal/BD foam-treated areas when compared to Cal/BD ointment
Koo et al.	[10]	NCT01536886 (LEO90100–35)	376	4 weeks		Phase II clinical trial	(i) mPASI values were significantly greater for Cal/BD foam when compared to Cal/BD ointment at week 1 ($p = 0.001$) and week 4 ($p = 0.005$) (ii) A higher percentage of patients in the foam treated group, experienced a regression or almost entirely regression of the skin lesions, in comparison to the ointment group (54.6% vs 43.0%; $p = 0.025$)

Table 1: Continued.

Authors	Reference	Study	Number of subjects	Treatment duration	Characteristics of the study	Main findings
				Foam vs gel		
Paul et al. and Griffiths et al.	[12, 13]	NCT02132936 (PSO-ABLE)	463	4 weeks (Cal/BD foam) or 8 weeks (Cal/BD gel)	Phase III clinical trial	(i) Cal/BD foam had higher treatment success rates than Cal/BD gel (38% vs. 22%; $p < 0.001$) (ii) Cal/BD foam had higher mPASI75 rates than Cal/BD gel (52% vs. 35%; $p < 0.001$) (iii) Drug reactions were reported in 7.6% of Cal/BD foam patients versus 3.7% in the Cal/BD gel treatment group (iv) A higher rate of Cal/BD foam treated patients achieved 0/1 DLQI scores compared to Cal/BD gel patients at weeks 4 (45.7% vs 32.4%; $p = 0.013$) and 12 (60.5% vs 44.1%; $p = 0.003$) (v) Cal/BD foam treatment EQ-5D utility index values improvement is higher than in Cal/BD gel (0.09 vs 0.03; $p < 0.001$) (vi) Cal/BD foam treatment PQoL-12 utility index values improvement is higher than in Cal/BD gel (−2.23 vs −2.07; $p = 0.029$) (vii) Results on itch, itch-related sleep loss, and work impairment were better in patients treated with Cal/BD foam when compared with the gel alternative
Hong et al.	[14]	NCT02310646 (PSO-INSIGHTFUL)	213	1 week (Cal/BD foam for 1 week, followed by Cal/BD gel for 1 week, or vice versa)	Phase IIIb clinical trial	(i) Cal/BD foam and gel formulations resulted with half of the patients showing a preference for each of the formulations (50% vs 50%) (ii) Cal/BD foam was generally assessed as the preferred version by younger patients (aged 18–39 years), whereas Cal/BD gel tended to be selected by older patients (aged ≥40 years) (iii) Cal/BD foam and gel options rated high in the TPUQ and were preferred to other formulations

Table 1: Continued.

Foam vs cream						
Authors	Reference	Study	Number of subjects	Treatment duration	Characteristics of the study	Main findings
Hong et al.	[14]	NCT02310646 (PSO-INSIGHTFUL)	213	1 week (Cal/BD foam for 1 week, followed by Cal/BD gel for 1 week, or vice versa)	Phase IIIb clinical trial	(i) Great improvement in satisfaction when patients switched from ointment or cream formulations to the gel or foam versions of the Cal/BD treatment
Maintenance treatment						
Authors	Reference	Study	Number of subjects	Treatment duration	Characteristics of the study	Main findings
Stein Gold et al. Lebwohl et al. Papp et al. Kircik et al. and Jalili et al.	[22–26]	NCT02899962 (PSO-LONG)	521	52 weeks	Phase III clinical trial	(i) Long-term, proactive management of Cal/BD foam was associated to superior health outcomes and an increasing the time of the first relapse manifestation than conventional reactive management (ii) Remission duration in patients in the proactive treatment group was 41 days longer than in patients assigned to the reactive treatment group ($p < 0.001$) (iii) No clinically significant HPA-axis suppression was observed in either the reactive or proactive therapy groups after 52 weeks (iv) Both proactive and reactive Cal/BD treatment had a comparable safety profile (v) Proactive Cal/BD foam was associated with longer median time to first relapse (111 versus 31 days), reduced risk of first relapse ($p = 0.029$) and a greater proportion of days in remission (17%) (vi) No dryness (97.0% vs 95.6%), no erosion (98.9% vs 99.0%), no erythema (96.2% vs 96.1%), no oedema (98.7% vs 98.6%) and no burning/pain (96.6% vs 92.8%) were reported by the patients in both proactive and reactive Cal/BD treatment (vii) Proactive Cal/BD foam treatment exhibit a significantly greater improvement during all the time-points measured in the study compared to the reactive therapy, with a 15% lower values of DLQI ($p = 0.007$) and PSI ($p = 0.0128$) and a numerically lower EQ-5D-5L-PSO mean area under the curve score ($p = 0.0842$)

Table 2: Summary of findings of other studies (no clinical trials) comparing Cal/BD formulations.

Cal/BD foam versus either component alone							
Authors	Reference	Study	Number of subjects	Treatments	Treatment duration	Study type	Main findings
Stein Gold et al.	[27]	NCT01536886 (LEO90100–35), NCT01536938 (LEO90100–7), NCT01866163 (PSO-FAST)	Cal/BD aerosol foam ($n = 564$), BD aerosol foam ($n = 101$) and Cal aerosol foam ($n = 101$)	Cal/BD foam, Cal foam, BD foam	4 weeks	Pooled meta-analysis review	(i) Treatment success was achieved by 51% of Cal/BD aerosol foam treated patients, versus 31% with BD aerosol foam and 15% with Cal aerosol foam (ii) Mean decreases in mPASI were higher with Cal/BD aerosol foam (72%) than with BD aerosol foam (53%) or Cal aerosol foam (43%). (iii) Mean decreases in PASI75 were higher with Cal/BD aerosol foam (51%) than with BD aerosol foam (34%) or Cal aerosol foam (18%)
Cal/BD foam vs other formulations Foam vs ointment							
Authors	Reference	Study	Number of subjects	Treatment duration		Characteristics of the study	Main findings
Duvetorp et al.	[11]	—	376	Up to 8 weeks (two 4-week cycles)		Cost-utility analysis	(i) Cal/BD foam formulation was predicted to be more cost-effective than Cal/BD ointment in the treatment of psoriasis vulgaris

Table 2: Continued.

Authors	Reference	Study	Number of subjects	Treatment duration	Characteristics of the study	Main findings
Foam vs cream						
Papp et al.	[15]	NCT01536938 (LEO90100–7), NCT01536886 (LEO90100–35), NCT01866163 (PSO-FAST), NCT02899962 (PSO-LONG), NCT03308799 (MC2-01-C2), NCT03802344 (MC2-01-C7)	1,093	4 weeks (Cal/BD foam) or 8 weeks (Cal/BD cream)	MAIC	(i) Greater mean improvements in mPASI using Cal/BD foam after 4 weeks when compared to 8 weeks of Cal/BD cream ($p < 0.01$) (ii) 4 weeks of Cal/BD foam was significantly more efficacious than 8 weeks of Cal/BD cream ($p < 0.01$) in inducing PGA success
Reich et al.	[16]	NCT03802344 (MC2-01-C7), NCT03308799 (MC2-01-C2)	717	4 weeks (Cal/BD foam) or 8 weeks (Cal/BD cream)	Common anchor approach	(i) Cal/BD cream (8 weeks) was on par with foam (4 weeks) on PGA treatment success ($p = 0.21$) (ii) Cal/BD cream (8 weeks) was on par with foam (4 weeks) on PASI75 response ($p = 0.27$) (iii) Treatment satisfaction results have shown a superiority of Cal/BD cream versus foam at week 1 in four domains (iv) A trend toward improved QoL with the Cal/BD cream (8 weeks) vs the foam formulation (4 weeks)
Bewley et al.	[28]	NCT03802344 (MC2-01-C7), NCT03308799 (MC2-01-C2), NCT02132936 (PSO-ABLE), NCT02310646 (PSO-INSIGHTFUL)	373	4 weeks (Cal/BD foam) or 8 weeks (Cal/BD cream)	MAIC	(i) Not statistically significant differences in PGA success, mPASI75 or DLQI outcomes between Cal/BD cream (8 weeks) and foam (4 weeks) (ii) After 1 week of treatment, patients perceive Cal/BD cream to be more appropriate than foam

Table 2: Continued.

Authors	Reference	Study	Patient satisfaction in clinical practice	Patient satisfaction in clinical practice		
			Number of subjects	Treatment duration	Characteristics of the study	Main findings
Velasco et al.	[29]	—	446	4 weeks	Retrospective observational study	(i) TSQM-9's domains data indicated that patients are satisfied with the Cal/BD foam treatment
Campanati et al.	[30]	LION	256	4 weeks	Prospective observational study	(i) Through PPQ, more than 90% of previously treated psoriasis patients assessed Cal/BD foam as more effective, simpler to use, and better tolerated than prior topical therapies
Navarro-Triviño et al.	[31]	—	65	12 weeks	Prospective observational study	(i) Patients exhibited high levels of treatment adherence (73.8%) to Cal/BD foam after 12 weeks (ii) 70.8% of the patients are satisfied with the Cal/BD foam
Rigopoulos et al.	[32, 33]	CELSUS	400	4 weeks	Prospective observational study	(i) Almost all patients (99.7%) were adhering to Cal/BD foam treatment (ii) The patients reported that treatment with Cal/BD foam was "very good" in terms of effectiveness (64.5%), tolerability (59.0%), ease of application (58.8%), and overall treatment satisfaction

significant changes in the mean levels of albumin-corrected serum calcium or the ratio of spot urinary calcium to creatine in any of the cohort groups, indicating that the treatments did not have a clinically meaningful impact on these markers. [12].

A subanalysis of the PSO-ABLE phase III clinical trial was carried out in order to evaluate the impact of foam and gel Cal/BD formulations on patients' QoL ($n = 463$), assessed by dermatology life quality index (DLQI), EuroQol-5 dimension (EQ-5D), and Psoriasis QoL (PQoL-12) [13]. Pruritus, sleep disruption caused by pruritus, and the impact of disease on working life were also assessed. At week 4, significantly higher proportions of Cal/BD foam treated individuals reached DLQI scores of 0/1 (45.7% vs. 32.4%; $p = 0.013$) and 1/2 (60.5% vs. 44.1%; $p = 0.003$), compared to the Cal/BD gel-treated cohort [13]. Cal/BD foam vs. superior to Cal/BD gel as regards improved EuroQol 5 dimension (EQ-5D) utility index values (0.09 vs. 0.03; $p < 0.001$) and improvement in PQoL-12 scores (−2.23 vs. −2.07; $p = 0.029$) [13]. Also, results on work impairment, itch, and itch-related sleep loss were better in the cohort treated with Cal/BD foam when compared with the gel alternative. [13].

The PSO-INSIGHTFUL phase III trial investigated the vehicle preferences of 213 patients, comparing Cal/BD foam and gel formulations [14]. Preference for Cal/BD foam and gel formulations by patients reporting any preference was split (50% vs. 50%) [14]. Cal/BD foam and gel rated high in the topical product usability questionnaire (TPUQ), and were preferred to other formulations [14]. Finally, Cal/BD foam was commonly evaluated as the favored option by patients aged 18–39 years, while Cal/BD gel was more frequently chosen by patients aged ≥40 years [14].

3.3. Foam versus Cream. No head-to-head clinical studies comparing Cal/BD foam and cream have been published so far. However, the efficacy, patient satisfaction, and QoL for Cal/BD cream and foam formulations have been compared, using indirect analyses, in three recent studies [15, 16, 28]. It is usual to conduct indirect comparison analysis, particularly when side-by-side data are unavailable. Diverse health technology assessment (HTA) agencies, including those in the United Kingdom, Germany, and France, enable indirect comparison analyses. The European Network for Health Technology Assessment (EUnetHTA) has also provided explicit instructions for the use of various indirect comparison methods [16].

Papp et al. performed a matching-adjusted indirect comparison (MAIC) of efficacy outcomes in trials of Cal/BD foam and cream preparations for managing plaque psoriasis [15]. They used as outcomes the percentage of patients with Physician's Global Assessment (PGA) achievement and modified mPASI [15]. According to this analysis, individuals treated 4 weeks with Cal/BD foam were more likely to attain PGA achievement than after 8 weeks of Cal/BD cream, with greater average enhancements in mPASI ($p < 0.01$) [15]. Similar results were obtained in the MAIC unanchored analyses, where Cal/BD foam (4 weeks) was significantly more efficacious than Cal/BD cream ($p < 0.01$ in five of six comparisons) in inducing PGA success at 8 weeks. Average reductions in mPASI were significantly greater with Cal/BD foam than with Cal/BD cream in the unanchored analysis of this study [15]. Reich and collaborators also compared the efficacy, impact on QoL, and treatment satisfaction of patients with Cal/BD cream and foam formulations [16]. In this case, the authors used a common anchor approach to realize the comparison, using Cal/BD gel as comparator. Results from this indirect comparison analysis indicated that treatment with Cal/BD cream for 8 weeks was on par with foam Cal/BD foam for 4 weeks as regards PGA treatment success ($p = 0.21$) and PASI75 response ($p = 0.27$) [16]. Regarding treatment satisfaction, Cal/BD cream was better than Cal/BD foam at week 1 in four domains. In addition, there was a trend toward improved QoL with the Cal/BD cream vs. the Cal/BD foam formulation throughout the recommended duration of treatment [16]. However, the authors pointed out that the heterogeneity across the studied populations could be a potential effect modifier and add bias to the results of the research [16]. For instance, the compared studies had a different treatment time, 8 weeks for the Cal/BD cream and 4 weeks in the case of the foam formulation. It is worth mentioning that patients with "severe disease" were excluded from the Cal/BD cream studies, but not from the Cal/BD foam PSO-ABLE and PSO-INSIGHTFUL trials.

Bewey et al. performed another MAIC comparing Cal/BD cream vs. Cal/BD foam for the treatment of plaque psoriasis [28]. The authors did not find any significant differences between Cal/BD cream and foam, after their dosing schedule (8 and 4 weeks, respectively), as regards PGA success, mPASI75, or DLQI outcomes [28]. Regarding treatment satisfaction, the study concluded that, individuals perceive Cal/BD cream to be better suited than Cal/BD foam after 1 week of treatment [28].

The PSO-INSIGHTFUL clinical trial also collected data regarding patients' preference [14]; satisfaction was greatly improved when patients switched from previous ointment or cream treatments to the Cal/BD gel or foam formulations [14]. Patients were naïve to Cal/BD treatments.

4. Maintenance Treatment

Psoriasis lesions tend to relapse within months after treatment cessation and patients require maintenance therapy [36]. Several options, including biological and small-molecule systemic agents as well as topical treatment, are proposed for long-term psoriasis care [37]. Topical treatment is generally safe and, in most cases, less costly than systemic biological agents and small molecules, while providing positive outcomes in a broad spectrum of patients [37]. However, long-term flare management and prevention with topical treatment is considered an unmet need [38]. Many patients fail to achieve complete and persistent resolution of psoriasis lesions in the long term, resulting in a detrimental impact on patients' QoL and also because of the harmful effects of long-term administration of steroid-based treatments [39]. The PSO-LONG phase III clinical trial, which included a total of 521 randomized patients,

explored the long-term effect of Cal/BD foam applied twice weekly as proactive maintenance therapy for up to 52 weeks [22, 23]. Proactive management involves a continuous treatment that is carried out periodically even in the absence of lesions, as opposed to reactive treatment, consisting in application of topical treatment only to existent or emerging psoriasis lesions. In the PSO-LONG study, long-term, proactive management of Cal/BD foam (twice weekly) was associated to better health outcomes than conventional reactive management (flare treatment once daily for 4 weeks) and also increasing the time of the first relapse manifestation (+26 days) [23]. Moreover, over the course of one year, the duration of remission in patients in the proactive treatment group was 41 days longer than in patients assigned to the reactive treatment group ($p < 0.001$) [23].

As mentioned above, the negative effects of steroid-based topicals are seen as a significant obstacle to long-term usage [40]. For this reason, one of the aims of the PSO-LONG clinical trial was to evaluate the safety of long-term proactive therapy with Cal/BD foam in patients with severe psoriasis (PGA = 3 and BSA 10–30%). This profile of patients ($n = 66$) was selected because they are more vulnerable to corticosteroid-induced hypothalamic-pituitary-adrenal- (HPA-) axis suppression and systemic toxicity [22, 24]. After 52 weeks, no clinically significant HPA-axis suppression was observed. Moreover, no new concerns regarding safety were recognized, and both proactive and reactive Cal/BD options had comparable safety profiles. The efficacy of the two treatments was also evaluated in a subanalysis of patients with more severe psoriasis; among them, proactive Cal/BD foam was linked to an extended median time to first relapse (111 vs. 31 days), reduced risk of first relapse ($p = 0.029$) and a higher percentage of days in remission (17%) [24]. Therefore, proactive management of patients with Cal/BD foam outperforms reactive administration in terms of efficacy, with no impact on safety profile.

Another specific concern about long-term prescription of potent topical steroids is development of skin atrophy [41]. Another subanalysis of the phase III PSO-LONG trial determined the effect of proactive Cal/BD foam treatment compared to the reactive treatment on skin atrophy and local tolerability [25]. The vast majority of patients presented no dryness (97.0% vs. 95.6%), no erythema (96.2% vs. 96.1%), no erosions (98.9% vs. 99.0%), and no edema (98.7% vs. 98.6%) in any of the two Cal/BD treatment groups; in conclusion, skin atrophy was not observed at any point of the study, in either therapy group [25]. Furthermore, no burning/pain was reported by most patients (96.6% vs. 92.8%) [25].

Concerning long-term treatment effect on health-related QoL, a recently published post hoc analysis of the PSO-LONG study assessed the patient-perceived symptoms and patient-reported outcomes [26]. The proactive treatment strategy with Cal/BD foam outperformed the reactive strategy, with patients indicating improved and more persistent health-related QoL outcomes [26]. Patients experienced consistent improvement in DLQI, psoriasis symptom inventory (PSI), and EQ-5D scores, and the proactive treatment group exhibited significantly greater improvement at all the time-points measured in the study, with 15% lower values of DLQI ($p = 0.007$) and PSI ($p = 0.0128$) and a lower average area under the curve score of EuroQol-5D for psoriasis (EQ-5D-5L-PSO) ($p = 0.0842$) [26].

All available data from the PSO-LONG clinical study, which is the only study to date that evaluates the long-term use (52 weeks) of Cal/DB foam as maintenance treatment, indicate that it is effective and safe, and that proactive (twice weekly) treatment is superior to reactive treatment of lesions once daily for 4 weeks, leading to improved QoL. After the recently published results of the PSO-LONG trial, a recommendation to incorporate a preventive strategy for managing of mild to moderate psoriasis into clinical guidelines was made by an Italian consensus [42].

5. Patient Satisfaction in Clinical Practice

As previously commented, the success of a topical therapy is determined by different variables; among them, patients' adherence to treatment is of paramount importance [4], and directly related to patients' satisfaction [43–45]. Daily treatment routine may be time-consuming and inconvenient; moreover, some topical formulations may not be cosmetically acceptable to patients, impairing adherence to treatment [46]. In general, psoriasis patients are dissatisfied with their therapy, particularly those who get topical treatment, especially if they have moderate severity of disease [47, 48]. Since patient satisfaction is a key element of psoriasis topical therapy, it has been addressed in several research studies regarding topical Cal/BD foam.

Velasco and collaborators, in 2019, conducted a multicenter, cross-sectional, observational study in 88 Spanish clinics and hospitals with a total of 446 psoriasis patients [29]. In this study, the abbreviated version of the Treatment Satisfaction Questionnaire for Medication (TSQM-9), which compares present and previous patients' satisfaction with topical treatments, was used to evaluate the patients' satisfaction [29]. According to TSQM-9 effectiveness domain results, 37% of the patients were satisfied, 39% were very satisfied, and 12.7% were extremely satisfied with how well Cal/BD aerosol foam prevented or treated psoriasis. Regarding how well Cal/BD foam relieved psoriasis symptoms, the results were very similar: 36.1% of patients were satisfied, 36.7% were very satisfied, and 11.6% were extremely satisfied. Lastly, 82.8% of the patients were satisfied (34.8%), very satisfied (36.2%), or extremely satisfied (11.8%) with how quickly Cal/BD foam worked [29]. Regarding the convenience domain items, 89.9% of patients rated Cal/BD treatment as "good" [29]. Elevated levels of confidence and overall satisfaction were also seen: 75.3% of patients were very or extremely confident that using Cal/BD aerosol foam was beneficial for them, and 75.4% stated that they were very or extremely confident that the benefits of the treatment outweighed the drawbacks. As for the last item of TSQM-9, global satisfaction, 85% of patients stated they were satisfied (26.5%), very satisfied (45.8%), or extremely satisfied (12.7%) [29].

The LION study, performed in 17 dermatology clinics of Italy (256 patients), also used the TSQM-9 to evaluate patients' satisfaction regarding Cal/BD foam treatment [30].

The median ratings for efficacy, convenience, and overall satisfaction on the TSQM-9 were 83.3, 77.8, and 78.6, respectively [30]. The Patient Preference Questionnaire (PPQ) was used to determine patients' preferences in comparison to past treatments, according to the patient cohort, almost all the individuals (>90%) manifested Cal/BD foam to be easier to use, have higher effectiveness, and be better tolerated than prior topical therapies [30].

Navarro-Triviño et al. carried out a single-center, observational, noninterventional, prospective study on the satisfaction and adherence with daily use Cal/BD foam on 65 psoriasis patients [31]. At 12 weeks, treatment adherence was excellent in 73.8% of patients, and 70.8% were totally satisfied with the therapy [31].

The CELSUS study was a prospective and noninterventional research conducted in 23 locations in Greece and included 400 patients who were treated once daily with Cal/BD foam for a 4-week period [32, 33]. Reported results indicate that the 99.7% of patients in the cohort were compliant with the therapy. Moreover, the patients reported overall satisfaction with the Cal/BD aerosol foam formulation, specifically as regards ease of application, tolerability, and "very good" effectiveness [33].

A real-world data study conducted in Italy concluded that the topical use of Cal/BD aerosol foam for 4 weeks was able to relieve skin pain, thereby improving the quality of life of the study cohort, which consisted of 75 individuals [49].

6. Conclusions

In different clinical trials, greater efficacy has been shown by the Cal/BD foam formulation when compared to other formulations or to the individual components, and it also demonstrated a good safety profile, improvement in QoL, patient satisfaction, and cost-effectiveness. Long-term maintenance proactive treatment has been shown to be advantageous with respect to reactive treatment as regards time to relapse and duration of remission. Moreover, the effectiveness, patient satisfaction, and convenience of Cal/BD foam in the treatment of plaque psoriasis were confirmed by real life clinical studies.

Data Availability

No data were used to support the study.

Disclosure

The study sponsor had no role in the conception, the design of the study, or in the manuscript preparation.

Conflicts of Interest

LP has perceived consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Sandoz, Sanofi, and UCB. MP works in the Medical department of LEO Pharma Iberia.

Authors' Contributions

All authors have contributed to the idea, plan, search of literature, assessment, and classification of the data, and have participated in the writing and reviewing of the manuscript, approving the submitted version. All authors have agreed to the published version of the manuscript.

Acknowledgments

The authors thank Jesús Loureiro, PhD, for editing the manuscript and editorial assistance. Grammarly was used to check any grammatical errors in the text. This work was supported by Leo Pharma.

References

[1] M. Napolitano, F. Caso, R. Scarpa et al., "Psoriatic arthritis and psoriasis: differential diagnosis," *Clinical Rheumatology*, vol. 35, no. 8, pp. 1893–1901, 2016.

[2] M. Meier and P. B. Sheth, "Clinical spectrum and severity of psoriasis," *Current Problems in Dermatology*, vol. 38, pp. 1–20, 2009.

[3] J. Bagel and L. S. Gold, "Combining topical psoriasis treatment to enhance systemic and phototherapy: a review of the literature," *Journal of Drugs in Dermatology*, vol. 16, no. 12, pp. 1209–1222, 2017.

[4] L. F. Stein Gold, "Topical therapies for psoriasis: improving management strategies and patient adherence," *Seminars in Cutaneous Medicine and Surgery*, vol. 35, pp. S36–S45, 2016.

[5] S. Devaux, A. Castela, E. Archier et al., "Adherence to topical treatment in psoriasis: A systematic literature review," *Journal of the European Academy of Dermatology and Venereology*, vol. 26, no. s3, pp. 61–67, 2012.

[6] Y. Avazeh, S. Rezaei, P. Bastani, and G. Mehralian, "Health literacy and medication adherence in psoriasis patients: a survey in Iran," *BMC Primary Care*, vol. 23, no. 1, p. 113, 2022.

[7] B. Kuehl and N. H. Shear, "The evolution of topical formulations in psoriasis," *Skin Therapy Letter*, vol. 23, no. 4, pp. 5–9, 2018.

[8] C. Rogalski, "Calcipotriol/betamethasone for the treatment of psoriasis: efficacy, safety, and patient acceptability," *Psoriasis (Auckland, N.Z.)*, vol. 5, pp. 97–107, 2015.

[9] C. Queille-Roussel, M. Olesen, J. Villumsen, and J.-P. Lacour, "Efficacy of an innovative aerosol foam formulation of fixed combination calcipotriol plus betamethasone dipropionate in patients with psoriasis vulgaris," *Clinical Drug Investigation*, vol. 35, no. 4, pp. 239–245, 2015.

[10] J. Koo, S. Tyring, W. P. Werschler et al., "Superior efficacy of calcipotriene and betamethasone dipropionate aerosol foam versus ointment in patients with psoriasis vulgaris--A randomized phase II study," *Journal of Dermatological Treatment*, vol. 27, no. 2, pp. 120–127, 2016.

[11] A. Duvetorp, L.-Å Levin, E. Engerstedt Mattsson, and L. Ryttig, "A cost-utility analysis of calcipotriol/betamethasone dipropionate aerosol foam versus ointment for the topical treatment of psoriasis vulgaris in Sweden," *Acta Dermato-Venereologica*, vol. 99, no. 4, pp. 393–399, 2019.

[12] C. Paul, L. Stein Gold, F. Cambazard et al., "Calcipotriol plus betamethasone dipropionate aerosol foam provides superior efficacy vs. gel in patients with psoriasis vulgaris: randomized, controlled PSO-ABLE study," *Journal of the European*

Academy of Dermatology and Venereology, vol. 31, no. 1, pp. 119–126, 2017.

[13] C. E. Griffiths, L. Stein Gold, F. Cambazard et al., "Greater improvement in quality of life outcomes in patients using fixed-combination calcipotriol plus betamethasone dipropionate aerosol foam versus gel: results from the PSO-ABLE study," *European Journal of Dermatology*, vol. 28, no. 3, pp. 356–363, 2018.

[14] C.-H. Hong, K. A. Papp, K. W. Lophaven, P. Skallerup, and S. Philipp, "Patients with psoriasis have different preferences for topical therapy, highlighting the importance of individualized treatment approaches: randomized phase IIIb PSO-INSIGHTFUL study," *Journal of the European Academy of Dermatology and Venereology*, vol. 31, no. 11, pp. 1876–1883, 2017.

[15] K. A. Papp, H. Thoning, S. Gerdes et al., "Matching-adjusted indirect comparison of efficacy outcomes in trials of calcipotriol plus betamethasone dipropionate foam and cream formulations for the treatment of plaque psoriasis," *Journal of Dermatological Treatment*, vol. 33, no. 7, pp. 3005–3013, 2022.

[16] A. Reich, J. Selmer, J. Galván et al., "Efficacy, quality of life, and treatment satisfaction: an indirect comparison of calcipotriol/betamethasone dipropionate cream versus foam for treatment of psoriasis," *Current Medical Research and Opinion*, vol. 38, no. 9, pp. 1521–1529, 2022.

[17] M. Megna, E. Cinelli, E. Camela, and G. Fabbrocini, "Calcipotriol/betamethasone dipropionate formulations for psoriasis: an overview of the options and efficacy data," *Expert Review of Clinical Immunology*, vol. 16, no. 6, pp. 599–620, 2020.

[18] C. G. M. Gennari, F. Selmin, P. Minghetti, and F. Cilurzo, "Medicated foams and film forming dosage forms as tools to improve the thermodynamic activity of drugs to be administered through the skin," *Current Drug Delivery*, vol. 16, no. 5, pp. 461–471, 2019.

[19] M. Lind, K. T. Nielsen, L. H. Schefe et al., "Supersaturation of calcipotriene and betamethasone dipropionate in a novel aerosol foam formulation for topical treatment of psoriasis provides enhanced bioavailability of the active ingredients," *Dermatologic Therapy*, vol. 6, no. 3, pp. 413–425, 2016.

[20] Y. Tada, L. Iversen, and J. Koo, "Early efficacy and safety data with fixed-dose combination calcipotriol/betamethasone dipropionate foam attributed to mechanism of absorption and steroid potency," *Journal of the European Academy of Dermatology and Venereology*, vol. 35, no. S1, pp. 5–9, 2021.

[21] M. Lebwohl, S. Tyring, M. Bukhalo et al., "Fixed combination aerosol foam calcipotriene 0.005% (cal) plus betamethasone dipropionate 0.064% (BD) is more efficacious than cal or BD aerosol foam alone for psoriasis vulgaris: a randomized, double-blind, multicenter, three-arm, phase 2 study," *J Clin Aesthet Dermatol.*, vol. 9, no. 2, pp. 34–41, 2016.

[22] L. Stein Gold, J. Alonso-Llamazares, J. P. Lacour et al., "PSO-LONG: design of a novel, 12-month clinical trial of topical, proactive maintenance with twice-weekly cal/BD foam in psoriasis," *Advances in Therapy*, vol. 37, no. 11, pp. 4730–4753, 2020.

[23] M. Lebwohl, L. Kircik, J. P. Lacour et al., "Twice-weekly topical calcipotriene/betamethasone dipropionate foam as proactive management of plaque psoriasis increases time in remission and is well tolerated over 52 weeks (PSO-LONG trial)," *Journal of the American Academy of Dermatology*, vol. 84, no. 5, pp. 1269–1277, 2021.

[24] K. Papp, Z. Adamski, L. Guenther et al., "Efficacy and safety of proactive treatment with twice-weekly topical Cal/BD foam in patients with plaque psoriasis undergoing HPA-axis testing: a PSO-LONG subgroup analysis," *Journal of Dermatological Treatment*, vol. 33, no. 4, pp. 2297–2304, 2022.

[25] L. Kircik, M. H. Mørch, B. Petersen, M. Liljedahl, and A. Wollenberg, "Long-term treatment of plaque psoriasis with Cal/BD foam was locally well tolerated and not associated with skin atrophy," *AAD ePosters [Internet]*, vol. 85, no. 26260, 2022, https://eposters.aad.org/abstracts/26260.

[26] A. Jalili, P. Calzavara-Pinton, L. Kircik et al., "Quality of life and patient-perceived symptoms in patients with psoriasis undergoing proactive or reactive management with the fixed-dose combination Cal/BD foam: a post-hoc analysis of PSO-LONG," *Journal of the European Academy of Dermatology and Venereology*, vol. 36, no. 1, pp. 60–67, 2022.

[27] G. L. Stein, M. Lebwohl, A. Menter, J. Villumsen, M. Rosen, and J. Koo, "Aerosol foam formulation of fixed combination calcipotriene plus betamethasone dipropionate is highly efficacious in patients with psoriasis vulgaris: pooled data from three randomized controlled studies," *Journal of Drugs in Dermatology*, vol. 15, no. 8, pp. 951–957, 2016.

[28] A. Bewley, E. Barker, H. Baker et al., "An anchored matching-adjusted indirect comparison of fixed-dose combination calcipotriol and betamethasone dipropionate (Cal/BDP) cream versus Cal/BDP foam for the treatment of psoriasis," *Journal of Dermatological Treatment*, vol. 33, pp. 3191–3198, 2022.

[29] M. Velasco, D. González-Fernández, M. Rodriguez-Martín, M. Sánchez-Regaña, and S. Pérez-Barrio, "Patient and physician satisfaction with calcipotriol and betamethasone dipropionate aerosol foam in the treatment of plaque psoriasis on the body," *Actas Dermo-Sifiliográficas*, vol. 110, no. 9, pp. 752–758, 2019.

[30] A. Campanati, L. Atzori, C. Potenza et al., "Patient satisfaction with calcipotriol/betamethasone dipropionate cutaneous foam for the treatment of plaque psoriasis: the LION real-life multicenter prospective observational cohort study," *Dermatologic Therapy*, vol. 34, no. 5, Article ID e15077, 2021.

[31] F. J. Navarro-Triviño, M. Lozano-Lozano, and R. Ruiz-Villaverde, "Calcipotriol/betamethasone dipropionate aerosol foam for plaque psoriasis: a prospective, observational, non-interventional, single-center study of patient adherence and satisfaction in daily use," *Dermatology Practical and Conceptual*, vol. 11, no. 3, Article ID 2021056, 2021.

[32] D. Rigopoulos, E. Lazaridou, E. Papadavid et al., "Subpopulation analysis of patients with plaque psoriasis treated with calcipotriol/betamethasone aerosol foam; effectiveness and patient satisfaction, according to baseline disease severity and prior psoriasis treatment experience, in a Greek population," *Dermatologic Therapy*, vol. 35, no. 6, Article ID e15484, 2022.

[33] D. Rigopoulos, E. Lazaridou, E. Papadavid et al., "Patient-reported outcomes with calcipotriol/betamethasone aerosol foam in patients with plaque psoriasis in Greece. Results from the CELSUS study," *Journal of the European Academy of Dermatology and Venereology: JEADV*, vol. 35, no. 12, pp. e931–e934, 2021.

[34] K. Howard I Maibach and Z. S. Martin, "Scholtz–Dumas psoriasis small plaque bioassay," *Journal of Dermatological Treatment*, vol. 11, no. 1, pp. 15–19, 2000.

[35] G. Marsden and D. Wonderling, "Cost-effectiveness analysis: role and implications," *Phlebology*, vol. 28, no. 1_suppl, pp. 135–140, 2013.

[36] S. Bartos, D. Hill, and S. R. Feldman, "Review of maintenance of response to psoriasis treatments," *Journal of Dermatological Treatment*, vol. 27, no. 4, pp. 293–297, 2016.
[37] U. Mrowietz, "Implementing treatment goals for successful long-term management of psoriasis," *Journal of the European Academy of Dermatology and Venereology*, vol. 26, no. s2, pp. 12–20, 2012.
[38] S. Segaert, P. Calzavara-Pinton, P. de la Cueva et al., "Long-term topical management of psoriasis: The road ahead," *Journal of Dermatological Treatment*, vol. 33, no. 1, pp. 111–120, 2022.
[39] J. B. Rice, A. G. White, L. M. Scarpati, G. Wan, and W. W. Nelson, "Long-term systemic corticosteroid exposure: a systematic literature review," *Clinical Therapeutics*, vol. 39, no. 11, pp. 2216–2229, 2017.
[40] J. M. Carrascosa, C. Theng, and D. Thaçi, "Spotlight on topical long-term management of plaque psoriasis," *Clinical, Cosmetic and Investigational Dermatology*, vol. 13, pp. 495–498, 2020.
[41] E. Niculet, C. Bobeica, and A. L. Tatu, "Glucocorticoid-induced skin atrophy: The old and the new," *Clinical, Cosmetic and Investigational Dermatology*, vol. 13, pp. 1041–1050, 2020.
[42] C. De Simone, P. Dapavo, P. Malagoli et al., "Long-term proactive management of psoriasis with calcipotriol and betamethasone dipropionate foam: An Italian consensus through a combined nominal group technique and Delphi approach," *International Journal of Dermatology*, vol. 61, no. 12, pp. 1543–1551, 2022.
[43] L. Puig, J. M. Carrascosa, I. Belinchón et al., "Adherence and patient satisfaction with topical treatment in psoriasis, and the use, and organoleptic properties of such treatments: a Delphi study with an expert panel and members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology," *Actas Dermo-Sifiliográficas*, vol. 104, no. 6, pp. 488–496, 2013.
[44] M. Augustin, B. Holland, D. Dartsch, A. Langenbruch, and M. A. Radtke, "Adherence in the treatment of psoriasis: a systematic review," *Dermatology*, vol. 222, no. 4, pp. 363–374, 2011.
[45] A. Teixeira, M. Teixeira, V. Almeida et al., "Does the vehicle matter? Real-world evidence on adherence to topical treatment in psoriasis," *Pharmaceutics*, vol. 13, no. 10, p. 1539, 2021.
[46] A. Bewley and B. Page, "Maximizing patient adherence for optimal outcomes in psoriasis," *Journal of the European Academy of Dermatology and Venereology*, vol. 25, no. s4, pp. 9–14, 2011.
[47] O. D. van Cranenburgh, J. de Korte, M. A. G. Sprangers, M. A. de Rie, and E. M. A. Smets, "Satisfaction with treatment among patients with psoriasis: a web-based survey study," *British Journal of Dermatology*, vol. 169, no. 2, pp. 398–405, 2013.
[48] K. C. Duffin, H. Yeung, J. Takeshita et al., "Patient satisfaction with treatments for moderate-to-severe plaque psoriasis in clinical practice," *British Journal of Dermatology*, vol. 170, no. 3, pp. 672–680, 2014.
[49] L. Gallo, M. Megna, T. Cirillo et al., "Psoriasis and skin pain: real-life effectiveness of calcipotriol plus betamethasone dipropionate in aerosol foam formulation," *Journal of the European Academy of Dermatology and Venereology*, vol. 33, no. 7, pp. 1312–1315, 2019.