

REVIEW

A narrative review of fixed combination calcipotriol/betamethasone aerosol foam (Enstilar®) in the management of psoriasis with scalp involvement

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Abstract

The scalp is the most common site affected in patients with psoriasis with up to 80% of these patients having some degree of scalp involvement. In this narrative review, we evaluate available data on the use of an innovative aerosol foam formulation of calcipotriol plus betamethasone dipropionate (Cal/BD) to treat patients with psoriasis and scalp involvement. The full PubMed database was searched using the terms “calcipotriol”, “betamethasone dipropionate” and “aerosol foam”, and all articles relating to “psoriasis with scalp involvement” were retrieved and used in the preparation of this review. The evidence supporting the clinical effectiveness, tolerability and impact on health outcomes of Cal/BD aerosol foam in patients with scalp psoriasis was obtained from a phase II clinical trial and real-world evidence data from a non-interventional study as well as from two case series. The findings from

these studies show that Cal/BD aerosol foam is rapidly effective, improves skin condition, alleviates symptoms such as itch, and has a positive impact on patient quality of life. These attributes address several unmet needs for patients with psoriasis with scalp involvement and have the potential to improve individual adherence to treatment.

Keywords: aerosol foam, betamethasone dipropionate, calcipotriol, corticosteroids, psoriasis, real-world evidence, vitamin D analogues.

Citation

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Background

Psoriasis is a common chronic, immune-mediated inflammatory skin disease treated in daily dermatological practice, primarily characterized by sharply demarcated erythematous plaques with silvery white scaling.¹ The plaques can be localized on any skin region (e.g. elbows, knees and sacral area), but the scalp is the most frequently affected area.^{1,2} Approximately 2% of people in Western countries are diagnosed with psoriasis¹ and up to 80% of these individuals have some degree of scalp involvement.³

With respect to clinical presentation, scalp psoriasis can range from mild disease, which is associated with slight fine scaling similar to dandruff, to more severe forms,

where large areas of the scalp and beyond are covered in thick crusted plaques.⁴ In tandem with skin lesions, a number of debilitating symptoms, such as intense pruritus, soreness and scaling/shedding, commonly occur; less frequently, temporary hair loss and scarring alopecia have also been reported.^{1,4,5}

Psoriasis in general, and scalp psoriasis in particular, are both associated with signs and symptoms that can have a significant impact on the physical and psychological functioning of the affected individual.^{1,6-8} Itch, for example, is a frequent problem in all patients with psoriasis, and it markedly impacts the overall well-being, functioning and quality of life (QoL) of patients.^{9,10} This is exacerbated by the embarrassment and stigmatization caused by scalp lesions, which are difficult to hide, especially when they spread beyond the scalp area.

Consequently, scalp psoriasis can result in psychological distress, which has a marked deleterious effect on patient self-esteem and a detrimental impact on social functioning and interpersonal relationships.^{11–13} Moreover, the increased visibility of psoriatic scalp lesions (e.g. on the forehead, neck and ears) is a criterion used for the upgrading of severity grading of psoriasis.¹⁴

Many topical treatments have been used for psoriasis, including corticosteroids, dithranol, coal tar, vitamin D analogues and calcineurin inhibitors. In recent years combinations of a vitamin D3 analogue and a corticosteroid have been extensively studied, showing greater effectiveness than single-agent therapy.^{12,15,16} Clinical practice guidelines recommend the fixed-dose combination of calcipotriol (Cal) and betamethasone dipropionate (BD) for patients with mild-to-moderate psoriasis and as adjunctive therapy for those with more severe disease.^{11,15,17,18} The fixed-dose combination Cal/BD is now considered a gold standard in the initial treatment of psoriasis.¹⁸ For long-term treatment, after successful initial therapy, proactive management with Cal/BD fixed-dose combination twice weekly can be used to maintain disease control.¹⁸ In a phase III clinical trial, patients benefitted from long-term proactive management *versus* reactive management with Cal/BD aerosol foam regardless of baseline characteristics.¹⁹ The fixed combination of active ingredients can considerably inhibit active inflammation and facilitate the maintenance of a relapse-free state. By uniting the two active ingredients, the adverse events associated with corticosteroid and vitamin D analogue monotherapy, including skin atrophy and perilesional skin irritation, respectively, can be effectively reduced. Cal mitigates risks associated with BD and vice versa, resulting in the favourable safety profile observed with fixed-dose combination treatment.¹⁶

The primary objectives in scalp psoriasis treatment are alleviation of discomfort, reduction of symptoms and clearing of lesions. The selection of treatment options is mainly based on disease severity, with topical formulations being the mainstay for persons with mild-to-moderate disease.^{5,6} However, topical treatment on the scalp can be challenging due to poor accessibility, the presence of hair, the close proximity to facial skin and eyes and cosmetic reasons relating to the formulation used (which may be greasy/sticky and time-consuming to apply).^{11,15,17} To address some of the cosmetic challenges in psoriasis treatment, LEO Pharma developed an innovative aerosol foam formulation of a fixed-dose combination of Cal (50 µg/g) and BD (0.5 mg/g) (Cal/BD aerosol foam). This formulation, known as Enstilar® received its first approval in the USA in 2015. An important property of the alcohol-free foam formulation is that the active ingredients are thoroughly dissolved in the propellants butane and

dimethyl ether, creating a supersaturated solution. This is important because dissolved ingredients are the only ones able to penetrate through the skin barrier due to its integrity.^{20–22}

The efficacy and good tolerability of once-daily treatment with the fixed-dose Cal/BD aerosol foam was demonstrated in a clinical study programme involving large numbers of patients with psoriasis vulgaris.^{12,23–26} In these clinical trials Cal/BD aerosol foam resulted in more patients achieving treatment success (according to the Physician Global Assessment (PGA) scale) after 4 weeks than aerosol foam vehicle, BD aerosol foam and Cal aerosol foam alone, and after 8 weeks *versus* Cal/BD ointment or Cal/BD gel.²⁷

In this narrative review, we evaluate the evidence from early studies assessing the clinical attributes of the Cal/BD aerosol foam in patients with psoriasis with scalp involvement.

Search strategy

The full PubMed database was searched using the terms “calcipotriol”, “betamethasone dipropionate” and “aerosol foam”. A total of 78 records were identified; these were assessed for their suitability for inclusion in the review of the Cal/BD foam in patients with psoriasis and scalp involvement. Each reference was checked for suitability through a review of the published abstract or the full paper if needed. The search was augmented by references known to the authors.

Review

Clinical evaluation of the fixed-dose combination Cal/BD aerosol foam in patients with scalp psoriasis

As noted by Wang and Tsai in an evidence-based review of scalp psoriasis therapies, prospective clinical trials investigating treatments for patients with scalp psoriasis have been published infrequently.²⁸ The authors identified 44 suitable studies (27 randomized clinical trials, 4 pooled analyses, 10 open-label trials, 1 case series and 2 case reports); of these, 10 involved treatments with Cal/BD (gel or solution formulations).

Evidence pertaining to the clinical efficacy/effectiveness and tolerability of Cal/BD aerosol foam was derived from a 4-week phase II clinical trial on the treatment of psoriasis with Cal/BD aerosol foam compared with Cal aerosol foam and BD aerosol foam,^{12,29} and from real-world data, including a prospective non-interventional study as well as case reports and series,^{30,31} however, the evidence remains of a preliminary nature.

Findings from clinical trials – direct evidence

Lebwohl et al. reported findings for patients with both body and scalp lesions¹² and performed a sub-analysis specifically evaluating scalp psoriasis.²⁹ In this study, Cal/BD aerosol foam was compared with its individual components after 4 weeks of treatment in 302 adult patients with mild-to-severe psoriasis vulgaris of both the body and scalp (10.6%, 77.1% and 12.3% had mild, moderate or severe disease, respectively).¹² Some key findings are presented in Table 1. Treatment success was defined as 'clear' or 'almost clear' from baseline, as determined by the PGA. At week 1, Cal/BD aerosol foam resulted in a significantly higher success rate in the treatment of scalp psoriasis compared with Cal aerosol foam (26.0% versus 7.9%; $p < 0.001$) and BD aerosol foam (26.0% versus 13.9%; $p = 0.016$). At week 4, treatment success of the scalp was also significantly higher for Cal/BD aerosol foam than for Cal foam (53.0% versus 35.6%; $p = 0.021$) and numerically higher than BD aerosol foam (53.0% versus 47.5%; $p = 0.45$).

Real-world data

Randomized clinical trials are important to evaluate the efficacy, tolerability and safety of treatments. However, they are performed under ideal conditions and are generally designed to investigate very selective patient populations with strict monitoring and follow-up. Consequently, the findings from such trials often do not reflect results obtained from the more heterogeneous patient populations found in everyday clinical practice and in real-world situations, where treatments are administered to patients with a range of comorbidities or are receiving medications for other disorders.³² To bridge the gap between controlled clinical trials and real-world data, different types of publications based upon case studies/series, patient registries, medical records and observational studies have emerged. Data reported includes endpoints such as clinical effectiveness and safety, economic outcomes, patient-reported outcomes and health-related QoL. Real-world effectiveness studies can provide essential information regarding effectiveness

Table 1. Clinical findings from a randomized, double-blind clinical trial in 302 patients with psoriasis vulgaris of the body and scalp treated for 4 weeks with once-daily applications of fixed-dose Cal/BD aerosol foam, Cal aerosol foam or BD aerosol foam.^{12,29}

Parameter	Cal/BD N=100	Cal N=101	BD N=101
Withdrawal rate (%)	6.0	7.9	6.9
PGA body psoriasis			
Treatment success at week 1 (%)	6.0	2.0	4.0
<i>p</i> value versus Cal/BD	–	NS	NS
Treatment success at week 4 (%)	45.0	14.9	30.7
Odds ratio versus Cal/BD; 95% CI	–	4.34; 2.16–8.72	1.81; 1.00–3.26
<i>p</i> value versus Cal/BD	–	<0.001	0.047
PGA scalp psoriasis			
Treatment success at week 1 (%)	26.0	7.9	13.9
Odds ratio versus Cal/BD; 95% CI	–	4.13; 1.69–10.09	2.48; 1.18–5.22
<i>p</i> value versus Cal/BD	–	<0.001	0.016
Treatment success at week 4 (%)	53.0	35.6	47.5
Odds ratio versus Cal/BD; 95% CI	–	1.91; 1.09–3.05	1.24; 0.71–2.16
<i>p</i> value versus Cal/BD	–	0.021	0.45
PGA body and scalp psoriasis combined			
Treatment success at week 4 (%)	60.0	30.0	41.0
Odds ratio versus Cal/BD; 95% CI	–	3.74; 2.02–6.91	2.23; 1.26–3.97
<i>p</i> value versus Cal/BD	–	<0.001	0.005
Patient-rated severity of itch			
Visual Analogue Scale (points)	–43.4	–30.3	–44.8
Difference in itch intensity at week 4; 95% CI and <i>p</i> value versus Cal/BD	–	–15.3; –21.4 to –9.1	–3.2; –9.4 to 3.0
		<0.001	0.31

BD, betamethasone dipropionate; Cal, calcipotriol; PGA, Physician Global Assessment.

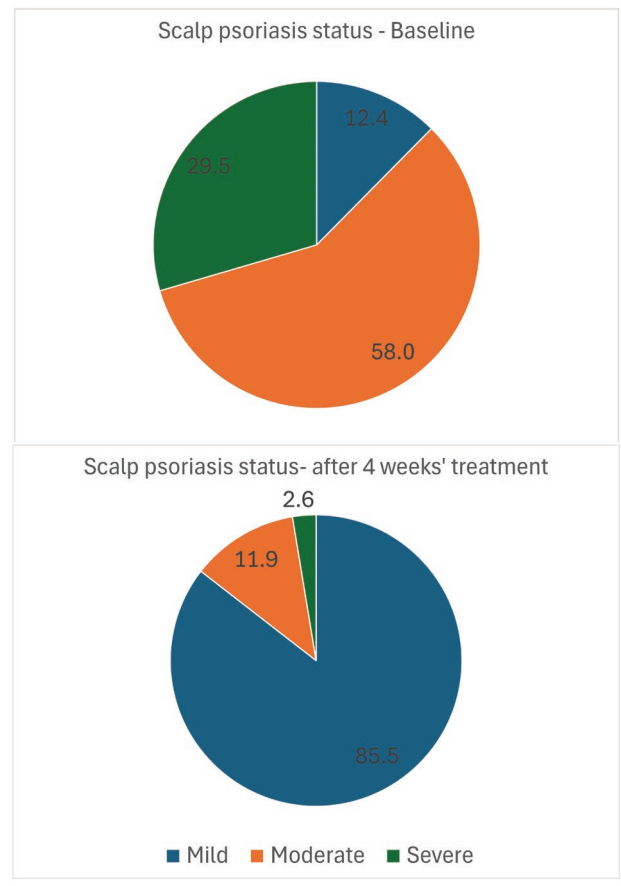
and safety in everyday clinical practice in diseases such as psoriasis, where QoL, patient perception and satisfaction, and social interactivity and workplace functionality are key outcome measures.

Non-interventional study – effectiveness and tolerability of Cal/BD aerosol foam in daily practice

In a prospective real-world study, a total of 217 adults with scalp psoriasis were treated with Cal/BD aerosol foam for 4 weeks in 96 German centres in everyday clinical practice.³³ The study confirmed the clinical benefits of the Cal/BD aerosol foam in terms of its effectiveness, rapid onset of action, good tolerability (rated as good to very good by >95% of physicians) and good safety profile. After 4 weeks, 53.4% of patients had achieved a scalp-body surface area <10% and mild scalp involvement in PGA. The proportion of patients with mild scalp psoriasis increased from 12.4% at baseline to 85.5% after 4 weeks (Figure 1 and Box 1). Patients rated their scalp psoriasis severity using six main symptom scores, and all scores were significantly improved ($p<0.001$) when comparing mean (\pm SD) values from baseline to after 4 weeks of treatment (Figure 2). Significant improvements were observed from the patient's perspective within 3 days of receiving treatment, and these improvements continued to increase throughout the 4-week treatment period.³³

The decrease in scalp psoriasis severity, as highlighted by reductions in lesion surface area and severity of symptoms corresponded with a significant enhancement in patients' QoL. This was evident through a reduction in the mean (\pm SD) Dermatology Quality of Life Index (DLQI) score from 9.6 ± 5.5 at baseline to 2.8 ± 3.5 after 4 weeks of treatment with Cal/BD aerosol foam ($p<0.001$). Throughout the study, the percentage of patients indicating that scalp psoriasis had a 'large to extremely large' impact on their QoL decreased from 39.3% to 3.8%, whilst the proportion reporting 'no or a slight influence' on their QoL increased from 27.9% to 82.3% (Figure 3).

Figure 1. Severity of scalp psoriasis measured using the Scalp-Physician Global Assessment (PGA) and other key findings at baseline and after 4 weeks of treatment with calcipotriol (50 µg/g)/betamethasone dipropionate (0.5 mg/g) aerosol foam (n=193); Scalp-PGA was assessed with the three categories 'mild/moderate/severe',⁵ with the category 'mild' being the lowest possible category to rank, thus also including 'clear' lesions.³³

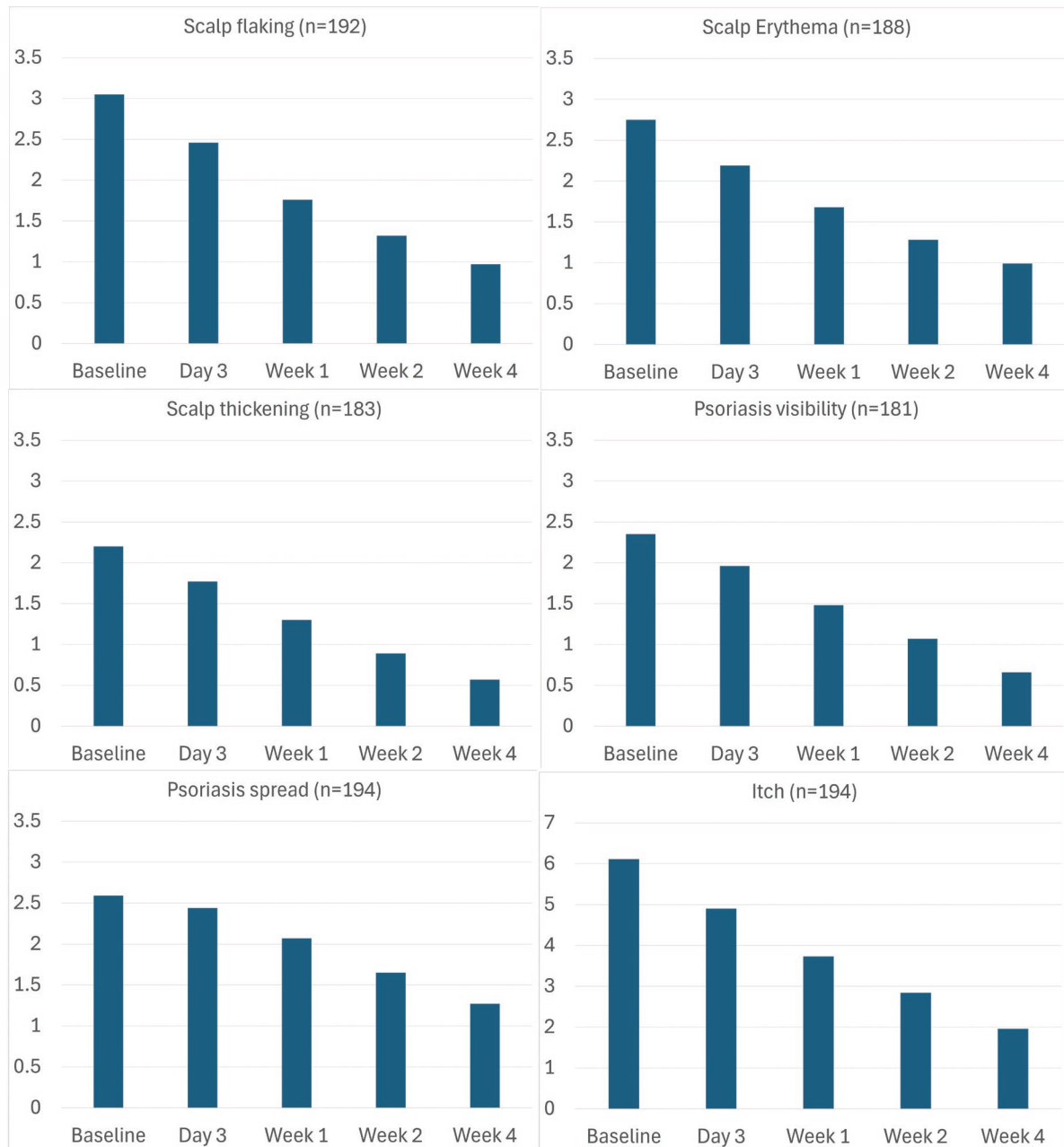


The Treatment Satisfaction Questionnaire-9 showed that patients were highly satisfied with the Cal/BD aerosol foam, with scores of 77.8 ± 24.2 for general satisfaction, 74.5 ± 27.1 for effectiveness and 72.0 ± 25.2 for ease of use.

Box 1. Other key findings.

- 53.4% of patients achieved a Scalp-Body Surface Area <10% (primary endpoint)
- 47.6% of patients achieved Psoriasis Scalp Severity Index score of ≤ 2 (primary endpoint)
- Mean \pm SD Scalp-Body Surface Area decreased from $32.5\pm 19.0\%$ (baseline) to $10.9\pm 12.5\%$ ($p<0.001$) after 4 weeks of treatment
- Patient-rated Global Assessment of the severity of scalp psoriasis decreased from 3.3 ± 0.9 points (baseline) to 1.3 ± 1.0 points ($p<0.001$) after 4 weeks of treatment
- Importantly, the symptom itch decreased from 6.1 ± 2.2 (baseline) to 2.0 ± 2.2 ($p<0.001$) after 4 weeks of treatment
- 69.1% of patients reported no or mild itching of the scalp by study end
- Overall, Dermatology QoL Index (DLQI) improved from 9.6 ± 5.5 (baseline) to 2.8 ± 3.5 at study end ($p<0.001$)

Figure 2. Mean symptom scores during the 4 weeks of treatment (last observation carried forward) for flaking, erythema, thickening and visibility (all rated from 0 = not at all to 4 = very), degree of spread (rated from 0 = 0% to 5 = 90–100%) and itch (rated from 0 = no itch to 10 = maximum itch); values at all timepoints were statistically superior to baseline with a p value of $p < 0.001$ with the exception of psoriasis spread after 3 days which had a p value of $p = 0.004$.³³

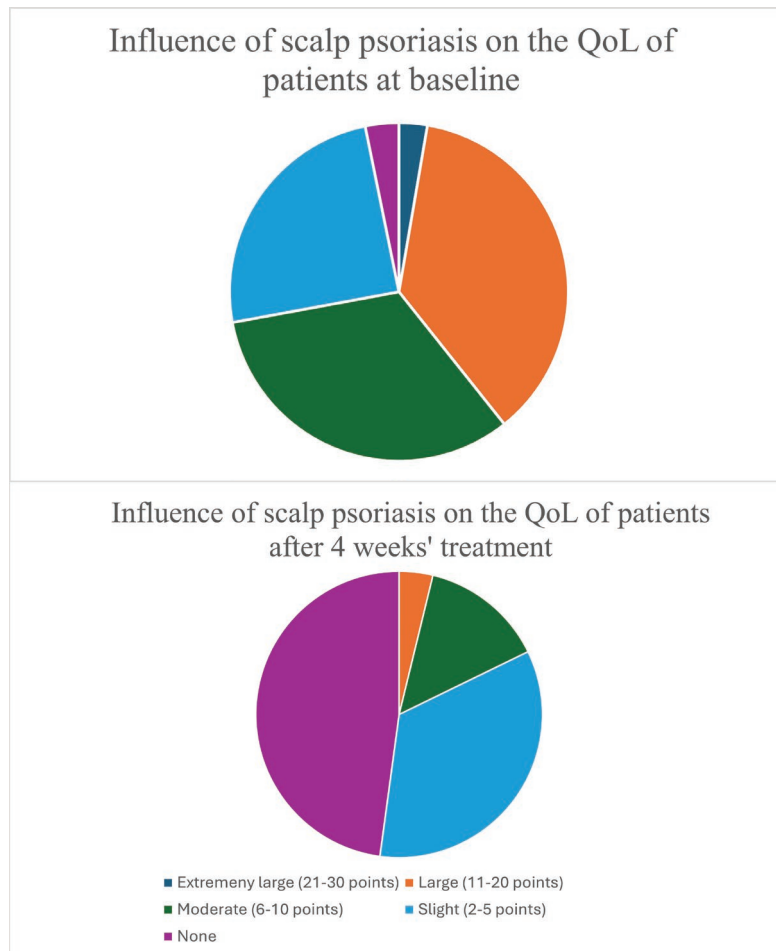


Symptom Change in symptom score over a 4-week period

Physicians rated the effectiveness of the Cal/BD aerosol foam formulation as good or very good for 92.7% of patients at the end of the study. No new safety concerns were identified. The authors concluded that this real-world, non-interventional study in everyday clinical practice “highlighted the clinical value of Cal/BD aerosol foam treatment in terms of its high effectiveness, rapid onset of

action (improved scalp symptoms within 3 days), good tolerability (rated as good to very good by 97.4% of physicians), and good safety profile in patients with scalp psoriasis”.³³ Interestingly, at the end of this study, 146 (74.1%) patients indicated that they wanted to continue treatment with Cal/BD aerosol foam, with 53.4% using it once daily, 23.3% twice/week and 23.3% as required.

Figure 3. Effect of scalp psoriasis on the quality of life (QoL) of patients (assessed using Dermatology Life Quality Index) at baseline and after 4 weeks of treatment with calcipotriol (50 µg/g)/betamethasone dipropionate (0.5 mg/g) aerosol foam (n=186).³³



Case studies

Case reports relating to the treatment of patients with psoriasis of the scalp with Cal/BD aerosol foam are summarized in Table 2. In a study involving 10 patients with scalp psoriasis, outcomes were categorized based on the severity of the condition prior to treatment. Results showed that the use of Cal/BD aerosol foam was highly effective in patients with mild ($n=2$) and moderate ($n=5$) disease, clearing lesions within 4 weeks from the start of treatment.³⁴ Amongst the three patients with severe psoriasis at baseline, the use of Cal/BD aerosol foam reduced the severity of the lesions to clear or mild in two cases and to moderate in the third case.

Three additional cases of scalp psoriasis were successfully treated with Cal/BD aerosol foam, as reported by Anderko et al.³⁵ The first two cases had recalcitrant disease and received various topical medications over a period of 15–30 years but experienced relief of symptoms

(itching) within 4 days of starting the Cal/BD aerosol foam and, after 4 weeks, the Psoriasis Area and Severity Index were markedly reduced and the lesions noticeably improved (Table 2). The last patient was previously untreated despite a 10-year history of scalp psoriasis and a Psoriasis Area and Severity Index of 15. Cal/BD aerosol foam resulted in almost complete clearance of scalp psoriasis as well as improvement of body lesions and QoL (DLQI reduced from a baseline score of 24 to 14 after 4 weeks).

Safety and tolerability

In three clinical studies, once-daily administration of Cal/BD aerosol foam for 4 weeks was well tolerated and did not present any new safety concerns.^{12,22,33} Between 97% and 99% of physicians rated the tolerability as good to very good with a low incidence of adverse events.^{22,36} These results are consistent with those for other topical formulations of Cal/BD as reported in systematic reviews, indicating that combination therapy holds a tolerability advantage over topical Cal monotherapy.^{37,38}

Table 2. Findings from case reports of patients with psoriasis of the scalp treated with Cal (50 µg/g)/BD (0.5 mg/g) aerosol foam.

Patient description	Outcomes
Three cases reported by Anderko et al. (2019)³⁵	
Case 1: woman, 29 years old, with moderate-to-severe recalcitrant scalp psoriasis for 15 years; previous treatments included various topical therapies (most recently clobetasol-17-propionate) and phototherapy. At presentation, her PASI was 11.4, the patient had marked psoriasis with infiltrating, adherent plaques, scaly skin and psoriasis capitis	Within 4 days of starting Cal/BD aerosol foam (once daily, at night) itching was reduced. After 4 weeks of treatment, scalp PASI was decreased to 1.6 and the scalp lesions were noticeably improved
Case 2: woman, 71 years old, with pronounced recalcitrant psoriasis confined to scalp for >30 years; various topical therapies had been tried previously (most recently BD plus salicylic acid). At presentation, her PASI was 4.8 and the patient had marked psoriasis capitis with multiple extensive infiltrates of adhering plaques	Within 4 days of starting Cal/BD aerosol foam (once daily, at night) itching was reduced. After 4 weeks of treatment PASI was decreased to 0.3 and the scalp lesions had almost disappeared
Case 3: man, 33 years old, with untreated psoriasis for 10 years. At presentation, plaque psoriasis was evident on the trunk, extremities and scalp, the PASI was 15; 20% of the BSA was affected (>50% of the scalp) and DLQI was 24	After 4 weeks of treatment with Cal/BD aerosol foam, partial skin clearance was achieved on the trunk and extremities (PASI 10, BSA 18%, DLQI 14) and the scalp was almost completely clear (Figure 3)
10 cases (3 groups) reported by Regnier and Trueb (2022)³⁴	
Mild scalp psoriasis (2 patients) previously treated with zinc pyrithione shampoo or topical corticosteroids	Cal/BD aerosol foam for 4 weeks completely cleared the scalp
Moderate scalp psoriasis (5 patients) previously treated with topical corticosteroids (n=4) with tar or ciclopirox olamine shampoo; one patient received only ciclopirox olamine shampoo	Cal/BD aerosol foam for 4 weeks completely cleared the scalp
Severe scalp psoriasis (3 patients) previously treated with a combination of topical corticosteroids or salicylic acid and a tar, zinc pyrithione, or selenium disulfide shampoo	After 4 weeks of treatment with Cal/BD aerosol foam, psoriasis improved by at least two points in all patients with two patients achieving clear or mild disease status and one achieving moderate disease status

BD, betamethasone dipropionate; BSA, body surface area; Cal, calcipotriol; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

Adherence to treatment

Adherence to treatment with topical therapies for chronic diseases, such as psoriasis, is a well-recognized important cause of treatment failure.³⁹ It has been estimated that between 39% and 73% of patients do not use their topical therapy as prescribed⁴⁰ and findings from a prescription database noted that 31% of 322 patients never collected their prescribed medications.⁴¹ Some patients are unintentionally non-adherent to treatment because of forgetfulness or a misunderstanding, whilst others are intentionally non-adherent because of perceived ineffectiveness, side-effects or some other reason. In a systematic review of topical medications used to treat psoriasis, adherence to treatment in real-life studies was much lower than that reported in clinical trials.³⁹ Reasons for non-adherence include low efficacy, perception of safety/tolerability, time-consuming

application, ease/convenience/frequency of application, cost and poor cosmetic characteristics.^{6,39}

In a large-scale multinational survey (n=3822) in which 71% of respondents indicated that psoriasis had a moderate to extremely high impact on their daily lives, the three primary reasons given for non-adherence to treatment were forgetfulness, using the medication only when necessary, and inconvenience.⁴² Regarding cosmetic characteristics, greasy ointments are difficult to apply and difficult to wash off the scalp/hair,^{43,44} whilst preparations like coal tar not only affect the appearance of the patient but are also messy and highly staining.^{6,45} The importance of the cosmetic acceptability of topical medications for each patient has driven the development of topical formulations that better meet these requirements.⁴⁶ In this regard, the novel Cal/BD aerosol foam

formulation is one of the more recent developments in the last decade. The accurate measurement of the Cal/BD aerosol foam adherence in patients with scalp psoriasis is yet to be determined. However, in two real-world studies conducted in daily practice, returned canisters were collected and showed reasonable adherence to treatment.^{22,33}

Conclusions

Optimal management of scalp psoriasis requires a comprehensive strategy that prioritizes attributes centred on patient needs. These include superior effectiveness, rapid onset of action, excellent tolerability and safety, and overall acceptability, all of which should lead to high levels of patient satisfaction, adherence to treatment and improved QoL. In this regard, topical treatment with a vitamin D analogue plus corticosteroid, such as fixed-dose Cal/BD, has become a well-established treatment for many patients with mild-to-moderate psoriasis of the scalp.

Over the last decade several new therapeutic formulations of Cal/BD have been developed and the topical aerosol foam formulation was approved by the FDA in the USA in 2015 and in the European Union in 2016. The early evidence with Cal/BD aerosol foam, as outlined in this review, shows that it is rapidly effective in reducing scalp lesions, alleviates symptoms such as itch, and has a positive impact on patient QoL. These attributes address several unmet needs for patients with scalp psoriasis and have the potential to increase patient adherence to treatment, which should facilitate improved long-term proactive treatment using a twice-weekly regimen. However, it should be noted that comparative studies with other approved formulations are needed to clarify the relative benefits of Cal/BD aerosol foam with other approved products such as Cal/BD gel and Cal/BD polyaphron dispersion cream, as well as with potential new products being developed. Ideally, this would include assessment of cosmetic acceptability and treatment adherence, which are key attributes for longer-term treatments in patients with scalp psoriasis.

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