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# THE EVOLUTION OF Cal/BD FIXED DOSE COMBINATION THERAPY FOR PSORIASIS: A CASE STUDY AND DISCUSSION

**Case Study:**

A fourteen-year-old boy presented with itchy thick red scaly plaques on his scalp, arms, legs, and torso. They had been present since the age of seven. The boy hid behind his long hair and made no eye contact with me; he was accompanied by his father who did all the speaking. The itching in his scalp was more intense than other areas. His only therapy at that point had been tar shampoo as well as topical steroid creams for his body, and neither offered much improvement in symptoms.

A family history revealed that his paternal uncle had severe psoriasis and psoriatic arthritis.

On physical examination, the patient had well-demarcated erythematous plaques with a thick silvery scale throughout the scalp, on the elbows, extensor forearms, knees, shins, and lower back. He was wearing a removable cast on his left forearm for a wrist fracture that had healed months ago. He was obese with a BMI of 43 and a BP of 140/80 mmHg. Blood work revealed a FBS 5.4 mmol/L, Cholesterol 5.61 mmol/L (↑ LDL, ↓HDL), Triglycerides 8.7 mmol/L, CRP 0.8 mg/L and elevated liver enzymes with suspected non-alcoholic steatohepatitis.

After discussion about the diagnosis and possible treatment options, the boy's father asked me if I could write a note to his teacher to exempt him from gym class as his son's classmates had been ridiculing him in the change room when they saw his skin condition on his arms and legs, which is why he had continued to wear his cast.

Psoriasis can have a tremendous impact on a child's physical, emotional and social quality of life.[1] For this particular patient, having psoriasis was devastating. In addition, his father felt the guilt of having passed this gene on to his son and the frustration of not having found adequate treatment to control his son's psoriasis over the previous 7 years.

A treatment option that was effective, safe, and easy to use leading to better adherence was the desired solution. As much as the patient was interested in clearing his skin quickly, his father was equally concerned about the long-term risks of therapy given his brother's long battle with severe disease associated with arthritis and some complications from systemic therapies he had used.

Parents may underestimate the emotional burden of psoriasis in their children and the requirement for counselling and support from their child's dermatologist.[1] After a long discussion focused on the skin condition itself and treatment options, calcipotriol/betamethasone dipropionate (Cal/BD) foam was prescribed for the patient's scalp and body plaques and a 1-month follow-up was arranged to discuss potential comorbidities.

This article will review some highlights of psoriasis in children and adolescents as well as the rationale behind potential therapeutic treatment options.

## Psoriasis

Psoriasis is a chronic, immune-mediated, genetic inflammatory skin disease that occurs in 2-3% of the Canadian population, which is comparable in incidence and prevalence to Europe and the USA.[3] It begins in childhood in almost a third of patients and the prevalence increases in a linear pattern from age 1 to age 18.[4] The incidence continues to increase from the 2nd decade reaching a peak in the latter half of the 6th decade. The global incidence of psoriasis has increased over the past 30 years in both adults and children, especially in North America and Western Europe.[5,6] As illustrated in this case, psoriasis is associated with comorbidities, such as hypertension, obesity, impaired glucose tolerance, hyperlipidemia, arthritis, and inflammatory bowel disease. These comorbidities occur in twice as many patients under the age of 20 with psoriasis as those without.[7]

The first line of treatment for mild-to-moderate psoriasis is topical therapy, which also complements systemic therapies in more severe disease.

## Rationale for Cal/BD Fixed Dose Combination

Until recently, topical treatment options included steroids and calcipotriol as monotherapy, as well as tar, anthralin, and tazarotene. A stable formulation containing both Cal/BD in an ointment base was developed more than 20 years ago. It was thought that this combination might yield superior efficacy and that the calcipotriol and the topical steroid would have complementary effects on psoriatic inflammation. It was also hypothesized that the local irritation caused by calcipotriol might be alleviated via the anti-inflammatory effect of the steroid and that the skin atrophy from the corticosteroid might be reduced via the use of a Vitamin D analogue.[8,9] (**Box 1** and **Table 1**) Having two active ingredients in a single formulation would also improve patient adherence.

In a double-blind study, 1106 patients were randomized to receive combination Cal/BD ointment, BD ointment or Cal ointment twice daily for 4 weeks. The primary efficacy endpoint clearly demonstrated that the combination treatment was more effective than the individual active components. The mean decrease in PASI from baseline to the end of the double-blind phase was statistically significantly greater in the combination group compared to both the betamethasone and calcipotriol groups and showed a more rapid onset of action with statistically significant differences in PASI evident after 1 week.[10]

In another study, 1,603 patients randomised to one of the 4 double-blind treatments used a regimen composed of a once daily application for 4 weeks with either Cal 50 mcg/g + BD 0.5 mg/g combination ointment, or BD 0.5 mg/g ointment or Cal 50 mcg/g ointment or ointment vehicle. The results demonstrated the superiority of the combination group to the other three groups with the mean decrease in PASI being evident in the combination

**Summary:** Combination Therapy has Complementary Effects on the Underlying Pathophysiology of Psoriasis, Resulting in Increased Therapeutic Response

**1.** As well as their normalizing effect on keratinocytes, vitamin D analogs, such as calcipotriol, exert immunomodulatory effects on Th1, Th2, Th17, and T-reg cells.

**2.** Corticosteroids, such as betamethasone dipropionate, combined with vitamin D analogs, additively inhibit Th1 and Th17 pro-inflammatory effects.

**3.** Calcipotriol induces an immunomodulatory Th2/T-reg cellular response, whereas corticosteroids suppress this effect, and combination treatment yields mild induction.

**4.** The preclinical results support the superior anti-psoriatic effect of corticosteroid and vitamin D analog combination treatment compared with monotherapies.

**Box 1.** Adapted from Segaert S, Shear NH, Chiricozzi A, et al., 2017.

**Table 1.** Summary of the effects of corticosteroids and vitamin D analogs in skin atrophy. Adapted from Segaert S, Shear NH, Chiricozzi A, et al., 2017.

| Mechanism | Effect of corticosteroids | Effect of vitamin D analogs | Overall clinical effect of combination treatment |
|---|---|---|---|
| Lipid synthesis | ↓ | ↑ | Prevents skin barrier and water loss impairment caused by corticosteroids. |
| AMPs, e.g., LL-37 | ↓ | ↑ | |
| KC proliferation' | ↓ | = | Attenuates epidermal thinning by corticosteroid-induced reduction of epidermal cells |
| Change in tissue modeling and structure:<br>- Hyaluronic acid<br>- Matrix metalloproteinases | ↓ | ↑ | Limits epidermal thinning from corticosteroid-induced loss of cellular volume |
| Collagen synthesis and turnover | ↓ | ↑ | Reduces dermal thinning caused by corticosteroid induced decrease in matrix network |
| Glycosamine synthesis | ↓ | ↑ | Increases water-binding capacity of the skin, decreasing corticosteroid-induced dermal thinning |
| Elastic fiber synthesis | ↓ | ↑ | Attenuates reduced skin flexibility/elasticity observed in topical steroidal monotherapy |

Downward arrow indicates downregulation; upward arrow indicates upregulation; equal sign indicates no effect; AMPs antimicrobial peptides; KC keratinocytes. * KC proliferation is psoriasis activity-dependent. The data presented here are based on non-inflamed skin.

group after only 1 week.[11] The mean decrease in PASI observed with the combination once-daily treatment in this study was similar to that seen with the combination twice-daily treatment in the previous study.

## Cal/BD Fixed Dose Combination in Pediatrics

The efficacy and safety of Cal/BD has also been demonstrated in a pediatric population.[12,13] In a study from 2014, seventy-three patients (mean age 10.8 years) with mild-to-moderate plaque psoriasis were treated with Cal/BD ointment for a median time of 35·0 weeks. At week 12, the mean PASI decreased 15·4% (from 5·2 to 4·4), BSA did not change in a meaningful manner, and median CDLQI decreased significantly from 5·5 to 4·0. VAS scores for pain and itch declined. At week 24, mean PASI decreased to 4·3 (17·3%). No related serious adverse events were observed in this study.[12] Another study assessed the safety of once-daily application of fixed-combination Cal plus BD gel in adolescent scalp psoriasis. Patients in this study were aged 12-17 years with moderate-to-very severe scalp psoriasis according to Investigator's Global Assessment (IGA) (≥ 10% of the scalp area affected). Results showed that 66 patients (85%) were clear or almost clear according to IGA. There was an 80% improvement in mean Total Sign Score from baseline to end of treatment. In total, at the end of treatment, 87% of patients rated their scalp psoriasis as clear or very mild, and 75 (96%) had no or mild pruritus compared with 14 (18%) at baseline (**Figure 1**).[13]

In a third study, the safety of the two-compound product, Cal/BD was assessed with results demonstrating that treatment up to 52 weeks appeared to be safe and well tolerated whether used on its own or alternating every 4 weeks with calcipotriol treatment.[14] This is welcome news given that psoriasis is a chronic, relapsing and remitting disease that requires long-term management.[14]

## Cal/BD Fixed Dose Combination in Scalp Psoriasis

Scalp psoriasis typically represents a therapeutic challenge. Itching and scaling represent the most distressing symptoms, and in some cases, scalp psoriasis can be associated with psoriatic alopecia, which can lead to scarring.[15] Patient adherence to therapy is also a challenge based on the type of vehicle (greasy vehicles are less acceptable), and ease and frequency of application.

A multicenter, randomized, double-blind study of 1504 patients with scalp psoriasis was conducted

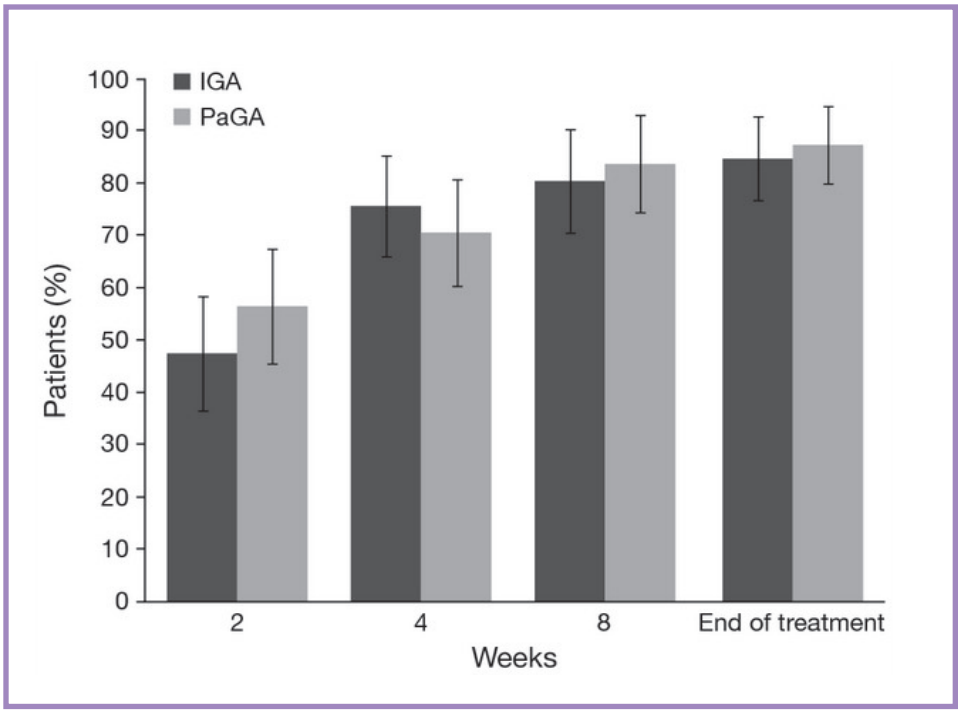


**Figure 1.** Proportions of patients experiencing treatment success as determined by Investigator's Global Assessment (IGA) and Patient's Global Assessment (PaGA) and 95% confidence intervals. Treatment success was defined by an assessment of clear or almost clear for IGA, or clear or very mild for PaGA. Week 8 data include only observed cases at that time point and end-of-treatment data include the last value recorded for that parameter; adapted from Gooderham et al, 2014.

to compare the clinical efficacy and safety of once-daily treatment for up to 8 weeks. The study randomized four treatments as follows: two-compound scalp formulation (calcipotriene 50 µg/g plus betamethasone 0.5 mg/g, as dipropionate) (n = 541), betamethasone 0.5 mg/g (as dipropionate) in the same vehicle (n = 556), calcipotriene 50 µg/g in the same vehicle (n = 272), or vehicle alone (n = 136). the The scalp formulation vehicle is less greasy than an ointment, which addresses patients' concerns around cosmetic acceptability. Patients who used the two-compound scalp formulation achieved "absent" or "very mild" disease more quickly than any other group, and this efficacy advantage became evident after only 2 weeks of treatment. The effect was achieved using an average of 20 g less medication over the full study period than in the BD group (p = 0.023), indicating a potential steroid-sparing effect of the two-compound scalp formulation.[16]

A 52-week, international, double-blind study of 869 patients with moderate-to-severe scalp psoriasis demonstrated a high level of safety and efficacy in long-term management of scalp psoriasis with the two-compound scalp formulation (Cal 50 µg/g plus BD 0.5 mg/g).[17]

## Cal/BD Aerosol Foam Formulation

To improve drug delivery further, an alcohol-free, surfactant-free aerosol foam formulation of Cal/BD, in which the active ingredients are dissolved in a mixture of volatile propellants (butane and dimethyl ether) to build a stable, supersaturated solution after the rapid evaporation of the propellants, was developed. The medication is in a non-skin-drying emollient vehicle in a pressurized spray can. This is associated with enhanced skin penetration and increased bioavailability.[18] The foam is to be rubbed gently onto affected areas once-daily with usage not exceeding 15 g daily. Clinical studies have shown Cal/BD aerosol foam to be more efficacious than the vehicle[19], more efficacious than Cal or BD aerosol foam alone[20] and more efficacious than Cal/BD ointment in patients with psoriasis vulgaris.[21,22] In the PSO-ABLE study, 4 weeks of Cal/BD aerosol foam was significantly more effective than 8 weeks of Cal/BD gel in patients with psoriasis (with lower drug consumption)[23]. This superiority was reached by week 1 and maintained throughout the 12-week treatment period.

Although the Cal/BD foam formulation has an increased bioavailability (as a result of the supersaturation and increased skin penetration), calcipotriol/betamethasone foam was not associated with an increased risk of treatment-related adverse events compared with the individual components as foam or the fixed combination as topical gel or ointment formulations.[24] In patients with extensive psoriasis vulgaris (15%-30% of body surface area, including ≥30% of scalp) who were treated once daily for 4 weeks, Cal/BD aerosol foam exhibited no clinically relevant impact on the hypothalamic–pituitary–adrenal (HPA) axis or calcium homeostasis. Results from this multicentre, single-arm, open-label, maximal-use systemic-exposure trial demonstrated that 49% of patients achieved treatment success (clear or almost clear status) when evaluated for efficacy. Cal/BD foam also demonstrated a favourable tolerability profile.[25]

The use of Cal/BD foam in adolescents is supported by a phase II, multicentre, prospective, open-label, non-controlled, single-group, 4-week trial in patients aged 12 to <17 years with plaque psoriasis on the body and scalp.[26] Results from this study show that Cal/BD foam is generally well-tolerated in adolescent patients. Over 4 weeks of treatment with Cal/BD foam, 32 treatment-emergent adverse events (AEs) occurred in 22 patients (20.8%), all but two of which were mild in severity (no treatment-emergent AEs were serious or severe). No treatment-emergent AEs led to study withdrawal or death. The most frequently reported AEs were upper respiratory tract infection [eight (7.5%)], nasopharyngitis [four (3.8%)], and acne [two (1.9%) and expected in this age group]. There was no evidence for dysregulation of calcium homeostasis or the HPA axis in patients with moderate disease. Limitations of this study include the fact that it was not designed to determine a maximum tolerated dose and the open-label design could not exclude the possibility of investigator bias. Additionally, the lack of a placebo control group impaired the determination of the true efficacy and safety of Cal/BD foam in adolescents and no patients in the HPA-axis cohort had a PGA of severe disease.

## Cal/BD Fixed Dose Combination in Elevated BMI

The use of Cal/BD foam in patients with an elevated BMI is supported by the sub-analysis from the PSO-FAST study demonstrating that Cal/BD aerosol foam, if used appropriately, is effective for the treatment of psoriasis independent of BMI and the extent or severity of disease.[27]

## Case Study (Continued)

The 14-year-old patient returned after four weeks of Cal/BD foam use with marked improvement of the scalp and skin plaques; but many challenges remained and had to be discussed, including the disease's potential to affect the cardiovascular system and metabolic pathways, as well as the lifelong psychosocial impact of psoriasis. Patients with early-onset psoriasis (age < 20 years) have been observed to be more anxious and depressed than patients with late-onset psoriasis.[28] The use of Cal/BD foam may provide substantial benefit to adolescent patients and the risk-benefit profile of initiating such therapy should be discussed with patients and their families to ensure optimal outcomes considering all aspects of the disease's impact on a patient's life.

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