Once-daily topical treatment for psoriasis: calcipotriene + betamethasone two-compound topical formulation

Jonisha Shepherd1
Arash Taheri1
Steven R Feldman1–3

1Center for Dermatology Research, Department of Dermatology, 2Department of Pathology, 3Department of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

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Background: Topical treatments are usually effective in mild psoriasis. However, the complexity of their use may result in low patient adherence with treatment. Combination of a vitamin D analog and a corticosteroid into a two-compound topical formulation has increased efficacy compared with either drug administered alone. Once-daily application of such a product would likely improve adherence. The purpose of this study was to determine whether twice-daily application of a calcipotriene + betamethasone topical formulation can provide improved clinical outcomes compared with once-daily treatment with the same product.

Methods: A review of the literature was performed seeking clinical trials comparing once-daily versus twice-daily application of calcipotriene + betamethasone topical formulations for the treatment of psoriasis.

Results: We found only one relevant clinical trial. This study showed similar efficacy and safety with once-daily versus twice-daily application of a topical calcipotriene + betamethasone formulation in the treatment of psoriasis vulgaris.

Conclusion: Once-daily application of a topical calcipotriene + betamethasone formulation may offer increased patient convenience and potentially increased patient adherence with long-term treatment, compared with twice-daily use, without reducing the efficacy. In order to enhance adherence, patient preference regarding frequency of application of topical treatments should be considered when prescribing medications.

Keywords: calcipotriene, betamethasone, once daily, twice daily, psoriasis, combination product

Introduction
The primary objective of therapy in mild-to-moderate psoriasis is to alleviate symptoms, achieve remission, and improve quality of life. Choice of treatment depends on factors such as severity of disease, extent and location of skin involvement, and presence or absence of other comorbidities, such as psoriatic arthritis. In mild-to-moderate psoriasis vulgaris, which accounts for most cases of the disease, treatment usually starts with topical preparations, including corticosteroids, vitamin D analogs, vitamin A analogs, and coal tar preparations. Topical treatments, if used correctly, are usually effective and safe in psoriasis. However, their expense and complexity of use may result in low adherence with treatment in the long term, which may lead to a reduction in efficacy.

Interventions to improve the efficacy of topical therapies would likely benefit from methods to improve adherence, as well as using more potent therapies.1,2 Combination formulations of topical medication can increase the effectiveness of available
treatments, probably through improving adherence of patients with treatment. In recent years, the combination of vitamin D analogs and corticosteroids into fixed two-compound topical formulations has increased the efficacy compared with either drug administered alone or even with nonfixed formulations of the active ingredients used in combination with each other. Although topical medications may be administered either once daily or twice daily, once-daily regimens of the topical drugs used to treat psoriasis may have better patient acceptance and compliance. Even the products which are not approved for once-daily treatment may actually be used once daily by many patients with poor adherence, even when they are prescribed for twice-daily short-term use.

Once-daily application of triamcinolone acetonide cream, betamethasone dipropionate ointment, and calcipotriene cream has had the same efficacy as twice-daily application for psoriasis vulgaris in clinical trials. In this study, we reviewed the literature in order to determine whether twice-daily or more frequent application of a topical calcipotriene (calcipotriol) + betamethasone formulation can provide a better clinical outcome than once-daily treatment with the same combination product.

Materials and methods
In this literature review, we searched Medline for articles published through September 2013. The search was performed using the terms (“calcipotriene” or “calcipotriol”) and (“betamethasone” and “psoriasis”) in the “title” of the articles. The search was confined to clinical trials. Studies comparing once-daily versus twice-daily or more frequent application of a calcipotriene + betamethasone topical formulation were included.

Results
Of 51 studies initially retrieved, two articles from one clinical trial were relevant and included.

In 2002, in an international, multicenter, prospective, randomized, double-blind, parallel-group, 4-week study, Guenther et al compared the clinical efficacy and safety of a combined ointment formulation of calcipotriene (calcipotriol) + betamethasone used once daily versus twice daily in psoriasis vulgaris. In total, 828 patients were included in this study. Of these, 150 patients received a combined formulation once daily (Dovobet ointment, calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g), 234 patients received the same combined formulation twice daily, 227 patients received calcipotriol 50 µg/g (Dovonex ointment) twice daily, and 207 patients used just vehicle twice daily. No statistically significant difference was observed in mean percentage change in the Psoriasis Area and Severity Index (PASI) from baseline to the end of treatment between the once-daily and twice-daily combined formulation groups. However, the PASI reduction was significantly greater in the combined formulation groups (68.6% once daily, 73.8% twice daily) than in the twice-daily calcipotriol group (58.8%) or the vehicle group (26.6%). The frequency of lesional/perilesional adverse reactions was similar in the combined formulation group and less than in the calcipotriol only group (9.9% combined formulation once daily, 10.6% combined formulation twice daily, 19.8% calcipotriol, 12.5% vehicle). The authors concluded that there was no statistically significant or clinically relevant difference in efficacy and safety between the combined formulations used once daily or twice daily. In this study, there was no statistically significant difference between the once-daily and twice-daily groups with regard to improvement in quality of life or the Psoriasis Disability Index.

Discussion
The increased rate of epidermal proliferation with impaired differentiation of keratinocytes in psoriasis is believed to be the result of dysfunction and overactivation of the immune system. Treatment of psoriasis is intended to decrease epidermal proliferation and the underlying inflammatory process. Topical corticosteroids and vitamin D analogs are usually considered to be the first-line treatment for mild plaque psoriasis. Topical corticosteroids have anti-inflammatory and antiproliferative effects. They are inexpensive, have a rapid onset of effect, and are relatively efficacious in psoriasis. However, long-term continuous use of superpotent formulations may be complicated by adverse effects, such as skin atrophy. Vitamin D analogs regulate the epidermal hyperproliferation and abnormal keratinization associated with psoriasis and provide better epidermal differentiation. They can also affect the local immune system by triggering apoptosis in inflammatory cells, inhibiting T helper (Th) 1 cytokine production, and induction of a Th1 to Th2 switch.

Vitamin D analogs do not induce skin atrophy and have a low rate of adverse events, with the most common being irritation, when compared with other topical treatments for psoriasis. Vitamin D derivatives have efficacy comparable with that of middle potency steroids; however, a disadvantage to using them alone is their slower onset of action.

Combination of a vitamin D analog and a corticosteroid into a two-compound topical formulation is more effective in reduction of epidermal and dermal T-cell markers and in
reduction of proliferation of epidermal cells than either drug used as monotherapy.\textsuperscript{14,15} This combination increases the efficacy of treatment for psoriasis vulgaris, although one clinical trial showed that it may not be as effective as clobetasol, which is a superpotent class I topical steroid.\textsuperscript{3,4,16,17} The probability of a $\geq 75\%$ reduction in PASI has been reported to be $47\%$–$50\%$ with once-daily calcipotriene + betamethasone ointment.\textsuperscript{5,18} Long-term as-needed treatment with a calcipotriene + betamethasone two-compound product for up to 52 weeks appears to be safe and well tolerated, with a less than $2\%$ risk of skin atrophy reported in the literature.\textsuperscript{19}

Once-daily application of a calcipotriene + betamethasone two-compound scalp formulation is a well tolerated, safe, and effective treatment option for scalp psoriasis, with more than $70\%$ of patients achieving cleared or minimal disease with 8 weeks of treatment.\textsuperscript{20} The two-compound scalp formulation is more effective in the treatment of scalp psoriasis than either of its individual components in the same vehicle.\textsuperscript{21–23} The calcipotriol + betamethasone two-compound ointment, applied once daily for 12 weeks can improve the Nail Psoriasis Severity Index in nail psoriasis by up to $70\%$.\textsuperscript{24}

In clinical trials, twice-daily treatment of psoriasis vulgaris for 4 weeks with calcipotriene + betamethasone ointment has provided a $74\%$ reduction in mean PASI score.\textsuperscript{25} In other studies, with once-daily application, a $71\%$ reduction in mean PASI score has been achieved in 4 weeks.\textsuperscript{26,27} Guenther et al could not find any difference in efficacy between once-daily and twice-daily application of calcipotriene + betamethasone ointment in psoriasis.\textsuperscript{10} The similar efficacy of the combined formulation observed with once-daily and twice-daily application favors recommending once-daily use as standard treatment, especially for long-term therapy. Once-daily monotherapy with betamethasone ointment or calcipotriene cream has also had the same efficacy for psoriasis vulgaris as twice-daily application of the same drug in clinical trials.\textsuperscript{3–9} To our knowledge, there is no evidence showing that more than once-daily application of any antipsoriatic drug can be more effective than once-daily use.

**Conclusion**

Once-daily use of topical medications, including calcipotriene + betamethasone combination products, in psoriasis can help simplify the treatment regimen and offer increased patient convenience and potentially increased patient compliance with long-term treatment. In order to enhance adherence and achieve an optimal treatment response, patient preferences for type of vehicle, concerns regarding speed of improvement versus overall safety profile, cost, and frequency of application should be considered when prescribing topical treatments.

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