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REVIEW

Calcipotriene/betamethasone dipropionate for the treatment of psoriasis vulgaris: an evidence-based review

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Abstract: While topical medications remain the cornerstone of the psoriasis treatment paradigm, they also come with the risk of multiple side effects. An alternative topical treatment option, calcipotriene or calcipotriol, is a vitamin D derivative that is thought to work by inhibiting keratinocyte proliferation and enhancing keratinocyte differentiation. Multiple studies have demonstrated its efficacy and safety in improving psoriasis when used in combination with topical corticosteroids. Given the effectiveness and side effect profile seen with this combination of topical steroid and calcipotriene, the US Food and Drug Administration approved a calcipotriene/betamethasone dipropionate product for use in psoriasis patients over the age of 12 in 2006. Our paper seeks to review clinical trial evidence of this combination medication and its use in the treatment of psoriasis vulgaris. While assessment of available evidence indicates that the topical medication is both safe and effective for the treatment of psoriasis vulgaris, addressing limitations of what is known, such as tolerability, adherence, and patient preference, of this combination drug in future high-impact studies is needed.

Keywords: calcipotriene, betamethasone diproprionate, psoriasis, topical treatment, steroids, vitamin D

Background

Psoriasis vulgaris is the manifestation of inappropriate immune activity against self-antigen and other harmless agents.[1] It has a multifaceted origin, with possible contribution by both genetic and environmental factors, although the evidence for environmental contribution has only recently been established and studied.[2] In nearly 40% of patients suffering from psoriasis or psoriatic arthritis, there is a history of similar illness in a first-degree relative.[3,4] Along with genetic predisposition, proposed risk factors for psoriasis vulgaris include stress, previous or concurrent infection, smoking, diet, drugs, and alcohol consumption.[5] The risk of psoriasis is directly associated with body mass index, with the risk being greater in individuals with higher body mass index.[6] Cardiovascular risk factors, such as hypertension and hyperlipidemia, are also more prevalent in patients with psoriasis.[7]

Psoriasis vulgaris is characterized by well-demarcated, pruritic and erythematous papulosquamous plaques, usually with white or silver scaling. Plaques can be of various sizes and thickness and can arise in a multitude of locations. Often, features of plaques can be site-specific. Those in intertriginous sites are typically without scale, while those on the knees and elbows are usually accompanied by heavier scaling.[8] Distribution of plaques and age of onset varies by patient, though both may be influenced by

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genetics.[9,10] HLA-C typing of multiple patients has revealed patterns in HLA-C type and age of onset, plaque location, and disease severity.[10]

Prior to recent research regarding its immune-mediated activity, psoriasis was believed to be a disease solely of the epidermal keratinocytes due to the increased proliferation and turnover of keratinocytes that is present in disease.[11] The dramatic increase in keratinocyte proliferation in psoriasis leads to skin thickening, which brings about visible, characteristic plaques.[12] The overall acceleration also results in dermal angiogenesis, which not only gives plaques an erythematous appearance but also allows for an increased flow of inflammatory cells to the affected area.[12] There is now a great deal of research that indicates the contribution of several immune components, such as T-cells and dendritic cells, to its pathogenesis.[8] Several cytokines are present in elevated amounts in psoriatic lesions, and concentrations of these cytokines found in serum is analogous to the severity of disease.[12] There is also an increase in immune cells, such as inflammatory myeloid dendritic cells, which results in a cytokine storm that perpetuates the inflammatory response seen in psoriasis patients.[13]

Despite the identification of these specific cytokine pathways and new targeted systemic therapies, topical medications remain the cornerstone of the psoriasis treatment paradigm. Noncombination topical treatment options have traditionally been used for psoriasis lesions. Due to their anti-inflammatory effects, topical corticosteroids have been the mainstay option for patients of all ages.[14] However, these medications come with a side effect profile that can cause thinning of the skin, striae, and possible tachyphylaxis with chronic use.[14] Topical steroid use can also be accompanied by the phenomenon known as steroid phobia, with patients themselves being fearful of using these medications and thus not adhering to their prescribed treatment regimen.

An alternative topical treatment option, calcipotriene or calcipotriol, is a vitamin D derivative that is thought to work by inhibiting keratinocyte proliferation and enhancing keratinocyte differentiation.[14] In two systematic reviews of calcipotriene's randomized controlled trials, calcipotriene was found to be more effective than placebo and as effective as potent topical steroids. Further studies demonstrated the use of calcipotriene in combination with topical corticosteroids was more effective in improving psoriasis than monotherapy with either agent.[14–18] These findings led to "sequential treatment," with the use of both medications together for several weeks, then pulsing the corticosteroid on weekends and using calcipotriene during the week, and eventually using calcipotriene alone. The main side effect of calcipotriene that can occur is perilesional skin irritation, but this rarely requires stopping treatment due to its severity.[14,16] Using topical steroids in combination with calcipotriene may help lessen this skin irritation.[14,16] Likewise, the use of calcipotriol also reduces the risks associated with betamethasone dipropionate, resulting in the favorable safety profile that is seen with fixed-dose combination treatment.[19] Of note, an immunomodulatory effect on immune cells by vitamin D and its analogs, such as calcipotriene, has been well documented in several experimental settings and clinical studies.[20–22]

The use of two agents complicates the treatment. Patients with psoriasis may be poorly adherent to even a single treatment. In addition, using two separate agents raises potential issues of compatibility and of unpredictable effects on absorption of the products. To address this, a combined topical corticosteroid/vitamin D analog combination drug was created. The additive and/or complementary effects in inhibiting proinflammatory mechanisms for the combination treatment have been described in different chronic inflammatory conditions, such as rheumatoid arthritis and psoriasis.[23–26,19] Given the efficacy and side effect profile seen with this combination of topical steroids and calcipotriene, in 2006 the US Food and Drug Administration (FDA) approved a calcipotriene/betamethasone dipropionate product for use in psoriasis patients over the age of 12. Our paper seeks to review clinical trial evidence of this combination medication and its use in the treatment of psoriasis vulgaris.

Evidence for this article was obtained through a PubMed search using the key words and phrases "calcipotriene, "betamethasone dipropionate," "psoriasis," "efficacy," "safety," and "combination therapy." Original articles and clinical trial data published within the last 5 years were given priority, as well as recent review articles. The authors' clinical experiences and professional opinions were drawn upon for a discussion within the Expert Opinion section.

Clinical trial data

There have been several clinical trials published evaluating the efficacy of a calcipotriene/betamethasone dipropionate combination as a treatment for psoriasis. Ten studies were published in total, evaluating the efficacy of calcipotriene/betamethasone dipropionate versus vehicle or monotherapies (Table 1). One of the earliest published studies evaluating the efficacy of the combined medication was conducted in 2002 with 1,603 study participants.[27] Subjects were randomized to a treatment that was used once daily for 4 weeks, with a primary endpoint of decreasing mean Psoriasis Area and Severity Index (PASI)

Table 1 Clinical trials evaluating the efficacy of calcipotriol/betamethasone dipropionate combination or treatment regimen

Study	Study type	n	Intervention	Results
Douglas et al[17]	DB, R	1,106	Treatment with combination, betamethasone dipropionate or calcipotriol twice daily for 4 weeks followed by maintenance with calcipotriol for 4 weeks	The mean percentage decrease in PASI due to the combination (–74.4) was greater than that of the monotherapies (–61.3 betamethasone and –55.3 calcipotriol)
Guenther et al[31]	R, DB, VC, PG, DC	828	Patients received treatment with combination once daily, combination twice daily, calcipotriol twice daily, or vehicle twice daily for 4 weeks	Use of the combined medication once or twice daily resulted in a significantly greater decrease in PASI than calcipotriol or vehicle only. No significant difference between once- or twice-daily use
Kaufmann et al[27]	R, DB	1,603	Calcipotriol/betamethasone dripropionate, calcipotriol, betamethasone dipropionate, or vehicle was used once daily for 4 weeks	Comparisons of the combined drug, each monotherapy, and the vehicle alone revealed that the calcipotriol/betamethasone dipropionate combination effectively lowered the mean PASI score more than the vehicle and each monotherapy
Papp et al[18]	R, DB, PG	1,028	Calcipotriol (50 μg/g)/betamethasone dripropionate (0.5 mg/g), calcipotriol, betamethasone dipropionate, or vehicle (ointment) was used once daily for 4 weeks	There was a significantly larger decrease in PASI due to the combined medication (73.2%) versus the betamethasone dipropionate (63.1%), calcipotriene (48.8%), and vehicle (28.8%)
Kragballe et al[32]	DB, DC	972	Subjects either used the combination once daily for 8 weeks followed by calcipotriol once daily for 4 weeks; combination once daily for 4 weeks followed by 8 weeks of calcipotriol ointment once daily on weekdays and the combined product once daily at weekends; or, calcipotriol ointment twice daily for 12 weeks	Subjects using the combined medication for 8 weeks daily had the greatest reduction in PASI and showed in the greatest improvement in disease condition at the end of 8 weeks
Saraceno et al[29]	DB, R	96	Calcipotriol/betamethasone daily for 4 weeks followed by calcipotriol for 8 weeks compared to 12 weeks of calcipotriol alone	Patients using the combined medication for 4 weeks had statistically significant clinical improvement compared with the group that used calcipotriol alone ($p< 0.001$)
Huang et al[33]	R, DB, AC, PG	320	Combination once daily with placebo once daily versus calcipotriol twice daily	Subjects using the combination had a greater decrease in psoriasis and PASI after 4 weeks than those using calcipotriol alone
Fleming et al[23]	R, PG, DB	364	Calcipotriol/betamethasone dipropionate, calcipotriol, betamethasone dipropionate, or vehicle (gel) was used once daily for 8 weeks	The combined medication had a significantly greater percentage of efficacy (27.2%) than the gel vehicle (0.0%), calcipotriol (11.4%), or betamethasone dipropionate (16.9%) monotherapy in gel
Ma et al[42]	DB, AC, PG	80	Once-daily calcipotriol/betamethasone with once-daily placebo versus twice-daily calcipotriol monotherapy over 12 weeks	Patients using the calcipotriene/betamethasone dipropionate still had greater reduction in PASI, area percentage of lesions, and VAS than those in the calcipotriol monotherapy group
Menter et al[28]	R, DB, VC	1,152	Calcipotriol/betamethasone dipropionate suspension gel, calcipotriol, and vehicle (gel) were used daily for 8 weeks	After 8 weeks, there was a significantly greater amount of subjects using the combined medication who achieved controlled disease compared to the monotherapy or vehicle arms

Abbreviations: AC, active-comparator; DB, double-blinded; DC, dose-comparison; PASI, Psoriasis Area and Severity Index; PC, placebo-controlled; PG, parallel-group; R, randomized; VAS, visual analog scale; VC, vehicle-controlled.

score. At the end of the study period, the combination was more effective than the vehicle (–48.3, $p<0.001$), calcipotriol alone (–25.3, $p<0.001$), and betamethasone dipropionate alone (–14.2, $p<0.001$). All comparisons revealed the calcipotriol/betamethasone dipropionate combination to be more effective than the vehicle and each monotherapy alone. A similar 2003 study (n=1,028) further confirmed that the combination medication was more effective in decreasing PASI (73.2%) than betamethasone dipropionate (63.1%), calcipotriene (48.8%), and vehicle (28.8%).[18]

Further studies were later done to optimize treatment and vehicle preparation. A 2010 study (n=364) evaluated the use of a gel vehicle as opposed to the previously studied ointment (Fleming et al [23]). For up to 8 weeks, a gel formulation of calcipotriol/betamethasone dipropionate was compared to the gel vehicle alone, calcipotriol in gel, and betamethasone dipropionate in gel. Efficacy was measured by the percentage of patients who were cleared of disease, had very mild disease, or a two-step improvement in 5-point Investigator's Global Assessment (IGA) by the conclusion of the study.

The combined medication showed that a significantly greater percentage (27.2%) of patients improved compared with the gel vehicle (0.0%), calcipotriol (11.4%) or betamethasone dipropionate (16.9%) monotherapy in gel. A following study (n=1,152) evaluated an additional topical suspension/gel formulation that was previously only used to treat scalp psoriasis.[28] This combination of calcipotriene/betamethasone dipropionate was again most effective in controlling disease compared to all other treatment groups, especially the vehicle control. Following the 8-week study period, there was a significantly greater number of subjects using the combined medication and who achieved controlled disease compared to those in the monotherapy or vehicle arms.

Comparisons of calcipotriol/betamethasone dipropionate with calcipotriol

A series of other studies focused on comparing the calcipotriol/betamethasone dipropionate combination with its individual active components have been published. In a 2002 study (n=1,106), patients were randomized to receive calcipotriol, betamethasone dipropionate, or the combination topically for 4 weeks.[17] Following the treatment, the group receiving the combination treatment displayed the largest decrease in PASI (–74.4%) compared to the betamethasone (–61.3%) and calcipotriol (–55.3%) groups. There was also a statistically significant difference in PASI values between treatment groups after only one week of treatment. An additional study (n=96) similarly evaluated the use of the combined topical versus calcipotriol alone, and while both groups showed improvement, the combination ointment had greater efficacy and produced results in less time than could be maintained with calcipotriol.[29] Subjects were randomized to be treated with the combination for 4 weeks followed by calcipotriol for 8 weeks, or calcipotriol alone for 12 weeks. Patients using the combined medication had a statistically greater improvement in disease after 2 and 4 weeks compared to those on monotherapy alone ($p<0.001$). Many similar studies comparing calcipotriol/betamethasone dipropionate to calcipotriol have been completed, revealing similar results that indicate the combination is more effective than each component alone.[30]

To evaluate the impact of regimen on efficacy, studies were done evaluating treatment plans that use the combined medication versus a monotherapy. A 2002 study (n=828) evaluated the efficacy of a once-daily versus twice-daily treatment plan for the combined medication and calcipotriol ointment.[31] For both once- and twice-daily combination groups, the percent reduction in PASI was similar (68.6% and 73.8%, respectively), and there was generally no improvement by imposing a second dose. However, both groups using the combined medication had a greater reduction in PASI than the calcipotriol group (58.8%) and vehicle control group (26.6%, $p<0.001$). In a 2004 study (n=972) of treatment using calcipotriol/betamethasone dipropionate versus calcipotriol, the group using the combined topical again had greater improvement in PASI than individuals using calcipotriol either once or twice daily.[32] The study consisted of 3 groups: group 1 used the combined medication for 8 weeks daily, followed by calcipotriol daily for 4 weeks for maintenance; Group 2 used the combined medication daily for 4 weeks, followed by 8 weeks of calcipotriol once daily on weekdays and the combination once daily on weekends only; and the final group used calcipotriol only, twice daily for 12 weeks. At the end an 8-week period, subjects using the calcipotriene/betamethasone combination for 8 weeks (group 1) had the greatest improvement in PASI (73.3%). The percentage of patients at 8 weeks with absent or mild disease was also greatest in group 1 (55.3%) compared to groups 2 (47.7%) and 3 (40.7%).[32] Daily use of the combined medication for a longer period resulted in the greatest improvement. Another study (n=320), published in 2009, confirmed the outcomes of a once-daily calcipotriene/betamethasone dipropionate regimen versus a twice-daily calcipotriol regimen.[33] One group used the combined ointment medication once per day and placebo once per day, and a second group used calcipotriol ointment twice per day. After weeks 1, 2, and 4, patients using the calcipotriene/betamethasone dipropionate had greater reduction in PASI, area percentage of lesions, and visual analog scale than those in the monotherapy group. After 4 weeks, there was a 75% decrease in PASI in 73.03% of subjects using combination compared to 48.32% of subjects using calcipotriol monotherapy.[33]

The combination is well tolerated in patients with psoriasis vulgaris and has typically resulted in adverse effects (AEs) that were rare and nonsevere. Some of the most common AEs reported were minor skin irritations, such as erythema, pruritus, and burning near the site of application.[18,31] Some studies have reported that less adverse events were present as a result of the combined medication versus calcipotriol monotherapy.[17,31] In the Douglas study, 8.1% of subjects using the combination reported an AE, while 12.0% reported AEs using calcipotriol only. Subjects using betamethasone dipropionate reported the least AEs throughout the study (4.7%). Three subjects in the 2003 study by Papp et al[18] experienced cases of skin atrophy, one while using the combined medication and two while using the betamethasone dipropionate monotherapy. This issue resolved with

discontinuation of use. Overall, use of the combination has produced less AEs than use of calcipotriol alone, with many of them being minor and reversible.

Discussion

Calcipotriene/betamethasone dipropionate gained FDA approval in 2006 and is indicated for the treatment of psoriasis vulgaris in patients 12 years of age and older. It is a combination product containing a fixed combination of 0.005% calcipotriene hydrate, a synthetic vitamin D3 analog, and 0.064% betamethasone dipropionate, a synthetic corticosteroid, in either a foam, gel/suspension, or ointment formulation. It exerts its action via reducing hyperproliferation and promoting differentiation of keratinocytes, with the added benefit of steroidal immunoregulatory and anti-inflammatory effects.[34–36]

The recommended use of calcipotriene/betamethasone dipropionate is topical application to affected areas of the body once daily for up to 4 weeks. Application should be discontinued when psoriasis control is achieved. Per its prescribing information, it should be applied to no more than 30% of total body surface area or to use with occlusive dressings. The two-compound product should not be applied to the face, axillae, groin, or thin skin areas and is contraindicated in patients with a history of hypersensitivity to any of the components, patients with disorders of calcium metabolism, and patients with erythrodermic, exfoliative, and pustular psoriasis.[37,38] For patients ages 12–17 years, and patients 18 years and older, it is recommended not to exceed use of 60 g and 100 g per week, respectively. During the course of treatment, patients should be monitored for adverse drug effects, similar to corticosteroid monotherapy. Calcipotriene/betamethasone dipropionate is a pregnancy Category C drug, with no clinical studies examining its excretion in breast milk.[39,40]

Topical therapies are primarily used in the management of mild-to-moderate psoriasis; however, they are also employed as adjuvant therapy for resistant lesions or more extensive disease when used concomitantly with phototherapy or systemic agents.[41] Systemic agents are generally more expensive and more difficult to use over the long-term, with larger and generally more severe side effect profiles. Topical therapies typically have a more tolerable side effect profile with low systemic absorption; however, they often have vigorous regimens that are difficult for patients to maintain. Calcipotriene/betamethasone dipropionate is recommended for once-daily use, making it a practical option for patients, which simplifies the treatment regimen and improves patient compliance.

This single-agent combination drug has been examined extensively during the last several years, with studies demonstrating that once-daily topical application of the combination calcipotriene/betamethasone dipropionate is more effective than monotherapy with either component in patients with psoriasis vulgaris. The clinical trials included in this review are larger, well-designed, randomized, and nonrandomized double-blinded control trials with moderate-to-high-quality evidence. All clinical trials showed a high degree of consistency in the efficacy of the combination drug with statistically significant reduction in PASI or greater percentage of patients cleared of the disease.[17,18,27,29,31–33,23,42] Different formulations of calcipotriene/betamethasone dipropionate are more efficacious in controlling disease than either monotherapy or vehicle control, which is in agreement with previous studies investigating optimization of treatment and vehicle preparation.[28,43]

The combination of both calcipotriene and betamethasone may also have a positive effect on increased adherence for patients with psoriasis, who often use a variety of medications as part of their treatment plan. Poor adherence to treatment plans may occur for a variety of reasons, one of which is a complicated regimen with multiple steps and multiple medications.[44] The more complex a treatment plan, the more time intensive and financially intensive it is, making adherence for patients increasingly difficult. The single-agent combination of topical steroid with vitamin D derivative has the advantage of improving adherence by allowing for only topical application of one medication rather than two. Furthermore, inconvenience, frustration with medication efficacy, as well as fear of side effects are also reasons cited by patients who do not follow their psoriasis treatment plans.[44–46] These reasons for nonadherence can be minimized through the use of the calcipotriene/betamethasone combination, as it reduces medication application time and may reduce fears about steroid side effects. Steroid phobia occurs with topical corticosteroids when patients are fearful of using these medications and discontinue treatment.[47] The use of the combination medication may help reduce these fears as it provides a topical medication that is safe for daily use and does not consist wholly of topical steroid. In addition to better adherence, another potential advantage of the combination drug is that it minimizes the unpredictability that accompanies the use of two separate topical medications, which could effectively change the vehicle and lead to unpredictable effects on absorption.

Calcipotriene/betamethasone dipropionate should be considered an initial therapeutic modality for psoriasis vulgaris as it is consistently effective and well tolerated. The greater tolerability and more favorable safety profile associated with the

combination medication, when compared to corticosteroid monotherapy, has been investigated. The probable mechanism is thought to be the ability of calcipotriene to counteract the atrophogenic effect of betamethasone on the skin through modulation of extracellular matrix components.[48] Patient preference and satisfaction with treatment has also been studied in regard to topical therapies and calcipotriene/betamethasone dipropionate, specifically. Individual patient choice should be considered, given the availability of different topical formulations that are efficacious, with the ultimate goal of improving treatment adherence, decreasing number of office visits, and lowering total health care costs.[49,50] Addressing limitations, such as tolerability, adherence, and patient preference, to effective use of this combination drug in future high-impact studies, is important to encourage better clinical outcomes. Recent studies have started investigating formulations such as the supersaturated alcohol-free aerosol foam, with a focus on optimizing the different calcipotriene/betamethasone dipropionate formulations.[51–53] Optimization of formulations, in order to maximize penetration and onset of action, for example, may further reduce health care expense and improve overall efficacy.

Disclosure

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