COMPARATIVE LONG-TERM SAFETY AND TOLERABILITY OF COMBINATION CALCIPOTRIOL/BETAMETHASONE DIPROPIONATE THERAPY IN SCALP PSORIASIS

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Abstract

Psoriasis of the scalp is widespread, hard to treat, and commonly has poor adherence due to difficulty with topical application and impact of cosmetic acceptability on continued usage. A two-compound scalp formulation containing calcipotriol and betamethasone dipropionate was also designed at a fixed dose to enhance the convenience and tolerability in addition to long-term safety. Methods: This was a long-term randomized comparative safety study, in which 900 adults with a minimum scalp psoriasis of moderate level were randomly assigned to two scalp formulation groups consisting of two compounds and calcipotriol monotherapy (nor 450). Routine clinical practice was followed with regard to the use of treatments once per day, as necessary, and with a 12-month follow-up. The variables of safety were withdrawals, adverse events, adverse drug reactions (ADRs) and events that were potentially linked to long-term exposure to corticosteroids on the scalp. Findings Baseline characteristics did not differ between groups. The percentage of patients who withdrew was less with the two compound formulation compared to calcipotriol (21.3% vs 39.8%) and less patients would have not been withdrawn because of the unacceptable adverse events and inadequate efficacy. The incidence of ADRs in both the two-compound formulation and calcipotriol were lower (17.1% vs 29.6%), as well as pruritus and skin irritation. Such a positive tolerability profile was sustained in exposure (0 to 6 months and 0 to 12 months) in patients who had prolonged exposure to treatment. Judged events which could have been associated with long-term corticosteroid use were rare and had a similar frequency in the groups. Conclusion: Long-term as-needed and once-daily use of the two-compound calcipotriol/betamethasone scalp formulation had a good safety and tolerability profile, decreased withdrawal rates and reduced ADRs than calcipotriol monotherapy without any observed increment in corticosteroid-associated scalp adverse events.

Keywords: Scalp psoriasis; Calcipotriol; Betamethasone dipropionate; Long-term safety

Introduction

Psoriasis is a chronic inflammatory skin disorder that is common in the west with a prevalence of about 2 percent. The most common of the many anatomical locations include the scalp, and over fifty percent of patients are affected in the head (1). Scalp psoriasis can be a source of significant psychological and social discomfort because it is very much visible and is accompanied by other symptoms like scaling and pruritus. Scalp psoriasis is also more difficult to manage as compared to lesions in other body locations mainly because of the barrier that hair establishes between the skin and topical drugs (2). Moreover, cosmetically unattractive formulations can decrease adherence of patients, even when they have sufficient therapeutic effect (3). Therefore, it is evident that there is a necessity to find a treatment option, which will be effective, safe, and cosmetically acceptable to achieve better compliance and therapeutic outcomes. Topical agents are still considered as the mainstay of the management of scalp psoriasis with vitamin D analogues and corticosteroids being the best-prescribed treatments (4,5). The antipsoriatic effect of calcipotriol, a vitamin D analogue, lies in its inhibitory effect on the proliferation of keratinocytes, the down-regulation of inflammation, and the normal epidermal differentiation. Its efficacy and safety in scalp psoriasis have been proven about its clinical use. One of the corticosteroids

is betamethasone dipropionate, which is a powerful steroid that is usually administered because of its fast anti-inflammatory effect. Nonetheless, the long-term corticosteroids treatment can be linked to local adverse effects, such as skin atrophy and follicular changes. In order to achieve the greatest efficacy and to reduce risk of steroid-associated side effects corticosteroids are often used with vitamin D analogue with complementary mechanisms of action (6). These combinations have the possibility of quick symptom response, long-lasting effectiveness, and less exposure to corticosteroids. In the past, combination therapy necessitated individual product applications with the scalp on a daily basis which was difficult to patients with scalp involvement (7-9). A 1-day simplified regimen is deemed more convenient and should lead to better compliance and clinical effectiveness. Calcipotriol and betamethasone dipropionate combination has shown positive safety and effectiveness in the treatment of psoriasis of the trunk and trunk and limbs. A more recent formulation that is specifically formulated to be applied to the scalp is a novel formulation. Rudimentary clinical trials have proven that combination of scalp formulation is effective, well tolerated and better than monotherapy with either of the components in the control of scalp psoriasis (10,11). Treatment needs to be repeated or long-term since the disease is chronic and relapsing, which is why the analysis of long-term safety is particularly crucial. The main aim of the current research was to measure the safety profile of the combined calcipotriol and betamethasone dipropionate scalp preparation in the context of prolonged use and in the environment that resembled a real clinical practice, where once-daily application of the preparation could be done when needed (12-14). The second goal was to compare its therapeutic effect to calcipotriol alone formulated in the same vehicle. To capture possible safety issues that may be related to the corticosteroid component more accurately, a non-steroidal comparator was chosen, which will allow identifying more negative effects that can otherwise be mischaracterized.

Methods

The study was a long term, randomized, comparative safety and tolerability trial with a two-compound topical formulation of vitamin D analogue and a corticosteroid or calcipotriol monotherapy in patients with scalp psoriasis. The trial was carried out in reference to the guidelines of Good Clinical Practice and other relevant ethical principles. Written informed consent was given by all the subjects before enrollment. Nine-hundred patients that reported a clinical diagnosis of scalp psoriasis were randomly assigned in a 1:1 ratio to the two-compound formulation or calcipotriol used alone. The centralized allocation system was applied to carry out randomization between the treatment groups to achieve equal distribution. The eligibility criteria included patients who are 18 years or above and due to scalp psoriasis, the severity must be at least moderate, according to the investigator. Major exclusion criteria were the existence of other serious dermatological conditions in the scalp or hypersensitivity to the study drugs known, or any other medical condition which may interrupt the study participation or safety evaluation. The affected areas on the scalp were treated top-down with study treatments once in a day by necessity, which mirrored the usual clinical practice. To promote consistent administration, patients were educated about the use of the techniques. Interruption or discontinuation of treatment may be done at clinical discretion, adverse events or patient choice. The total treatment and follow-up duration lasted to 12 months which permitted the assessment of short and long-term safety outcomes. The main aim of the research was to determine the safety of the long-term use of the two-compound formulation. The safety assessments involved the observation of adverse events, adverse drug reactions, and other events that were deemed to be potentially related to corticosteroid exposure (15). All adverse events were documented during the research and categorized by the severity and association with the treatment in the study. Special consideration was given to those reactions and events associated with the skin that could reveal the effects of corticosteroids on the scalp. The secondary objectives were the comparison of the withdrawal rates and motivations of discontinuing treatment between the two groups of treatment. The adverse drug reactions were evaluated in general and depending on the duration of exposure with references to evaluations at the first 6 months of treatment and evaluations up to 12 months of treatment among the patients whose time exposure was adequate. Patients might have more than one adverse event or cause of withdrawal and all the data reported were factored in the safety analysis. Regular visits to the study were used to document the

severity of the disease, the response to treatment and safety issues by the investigator. The set of safety analysis included all the randomized patients who had received one application of the study medication. Demographic information as well as baseline disease characteristics, adverse events, adverse drug reactions and withdrawal outcomes were summarized using descriptive statistics. The summaries of the continuous variables included means and SDs and the frequencies and percentages were used to summarize the categorical variables. Descriptive evaluation was used to compare the safety outcome across treatment groups to determine clinically significant differences in long-term safety and tolerability.

Results

The analysis set of safety involved 900 patients, and 450 patients per treatment group. The two groups balanced well in regard to baseline demographic and clinical characteristics (Table 1). The two-compound group and the calcipotriol group had similar age, and similar age distribution was exhibited in both groups. The proportion of male clients in each group was about 44 and most of the individuals were Caucasians. The average length of psoriasis was more than 17 years in each group, which was a long-term population. The severity of the disease measured by the investigator was similarly distributed with over fifty percent of the patients having moderate disease, twenty five percent having severe disease and the remaining five percent having very severe, indicating similar baseline disease burden in the treatments. The rates of withdrawal of the patients were found to differ significantly between treatment groups (Table 2). In general, fewer patients ceased treatment in the two-compound study group than calcipotriol group. Cessation caused by intolerability of adverse events and ineffectiveness of treatment were significantly lower in the two-compound group, but again, a larger percentage of the discontinuation was caused by these two factors in the calcipotriol group. Withdrawal rates based on loss to follow-up and voluntary discontinuation were not different in the groups. As much as patients might have reported multiple reasons behind their withdrawals, overall numbers of withdrawn patients were significantly low in the two-compound group, which suggests greater treatment tolerability and adherence. The frequency of adverse drug reactions (ADRs) was always lower in those patients who were exposed to the two-compound formulation than it was in patients who were exposed to calcipotriol monotherapy (Table 3). Generally, the number of patients who had at least one ADR was lower in the two-compound one. Such ADRs as pruritus, erythema, burning sensation, and skin irritation were not very common with the two-compound treatment. This positive safety profile was observed in the short-term (0 6 months) and long-term (012 months) exposure. The percentage of patients reporting any ADR in patients with long-term exposure was lower in the group of two compounds, and pruritus and skin irritation were significantly lower in the calcipotriol group. The adverse events that may be related to the use of long-term corticosteroids on the scalp were more uncommon in both groups (Table 4). The aggregate rate of corticosteroid-related incidences was minimal and similar across groups. Individual instances like folliculitis, dermatitis, acne, and rosacea were uncommon, and there was no statistically significant difference between the two-compound group. Notably, severe complications associated with corticosteroid were rare, which indicated that the two-compound formulation could be used as needed because of its safety in the long term. All in all, these results show that two-compound treatment is a good compromise of safety and tolerability with reduced rates of withdrawal and adverse drug reactions in comparison to calcipotriol monotherapy in long-term therapy.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Safety Analysis Set

Characteristic	Two-compound Group (n = 450)	Calcipotriol Group (n = 450)
Age		
Mean ± SD, years	48.6 ± 15.2	49.1 ± 14.6
Range, years	18–86	19–84
Sex		
Male, n (%)	199 (44.2%)	198 (44.0%)
Ethnicity		
Caucasian, n (%)	434 (96.4%)	437 (97.1%)
Duration of Psoriasis		
Mean ± SD, years	17.6 ± 13.5	17.5 ± 13.5
Range, years	1–66	1–72
Investigator's Assessment of Disease Severity		
Moderate, n (%)	250 (55.6%)	250 (55.6%)
Severe, n (%)	170 (37.8%)	170 (37.8%)
Very severe, n (%)	30 (6.6%)	30 (6.6%)

Table 2: Summary of Patient Withdrawals and Reasons for Discontinuation

Reason for Withdrawal	Two-compound Group (n = 450)	Calcipotriol Group (n = 450)
Unacceptable adverse events	9 (2.0%)	45 (10.0%)
Death[1]	1 (0.2%)	1 (0.2%)
Unacceptable treatment efficacy	15 (3.3%)	52 (11.6%)
Exclusion criteria emerging	5 (1.1%)	15 (3.3%)
Lost to follow-up	27 (6.0%)	30 (6.7%)
Other reason(s)[2]	25 (5.6%)	48 (10.7%)
Voluntary withdrawal	18 (4.0%)	19 (4.2%)
Total number of reasons for withdrawal[3]	**100**	**210**
Total number of withdrawn patients	**96 (21.3%)**	**179 (39.8%)**

Table 3: Summary of Adverse Drug Reactions During Short- and Long-Term Treatment

Adverse Drug Reaction	Two-compound Group (n = 450)	Calcipotriol Group (n = 450)
Any ADR	77 (17.1%)	133 (29.6%)
Burning sensation	4 (0.9%)	13 (2.9%)
Erythema	9 (2.0%)	15 (3.3%)
Pruritus	16 (3.6%)	45 (10.0%)
Psoriasis	11 (2.4%)	10 (2.2%)
Skin irritation	6 (1.3%)	25 (5.6%)
ADRs During 0–6 Months in Patients With ≥6 Months Exposure		
Patients with ≥6 months exposure	376	378
Any ADR	43 (11.4%)	85 (22.5%)
Erythema	4 (1.1%)	8 (2.1%)
Pruritus	7 (1.9%)	26 (6.9%)
Skin burning sensation	0	8 (2.1%)
Skin irritation	4 (1.1%)	16 (4.2%)
ADRs During 0–12 Months in Patients With ≥12 Months Exposure		
Patients with ≥12 months exposure	302	246
Any ADR	47 (15.6%)	65 (26.4%)
Burning sensation	3 (1.0%)	5 (2.0%)
Erythema	4 (1.3%)	5 (2.0%)
Pain of skin	3 (1.0%)	5 (2.0%)
Pruritus	6 (2.0%)	22 (8.9%)
Psoriasis	6 (2.0%)	3 (1.2%)
Skin irritation	3 (1.0%)	8 (3.3%)

Table 4. Incidence of Corticosteroid-Associated Scalp Adverse Events by Treatment Group

Event	Two-compound Group (n = 450)	Calcipotriol Group (n = 450)
Ocular hypertension	0	1 (0.2%)
Infected dermatitis	0	1 (0.2%)
Folliculitis	3 (0.7%)	3 (0.7%)
Impetigo	0	1 (0.2%)
Pustular rash	1 (0.2%)	0
Acne	1 (0.2%)	2 (0.4%)
Dermatitis	3 (0.7%)	1 (0.2%)
Rosacea	3 (0.7%)	5 (1.1%)

Discussion

The current long-term randomized comparative trial will have a substantial analysis of the safety and the tolerability of the two-compound scalp formulation of calcipotriol and betamethasone dipropionate in patients with scalp psoriasis under the conditions that are representative of real clinical practice (16,17). Since scalp psoriasis is a chronic, recurrent disease, and that often, the use of topical therapy is a long-term or recurrent process, the issue of long-term safety is critical when choosing a treatment method. The results of the current research indicate that the two-compound formulation has a good

safety profile with higher treatment adherence relative to the calcipotriol monotherapy, but with very few corticosteroid-related adverse events (18). There was good balance in baseline demographic and clinical features in both treatment groups, which meant that there was no likelihood of subsequent safety outcomes being affected by confounding disparities in patient populations. The study cohort was mainly made up of patients who had a long history of psoriasis and moderate to severe involvement of the scalp, which is a clinically significant population that is often encountered in the dermatological practice. This increases the extrapolation of the results to the actual management of scalp psoriasis. The incidence of treatment discontinuation was lower in patients undergoing the two-compound formulation than the incidence in patients undergoing calcipotriol therapy. It is important to note that the two-compound group had lower levels of withdrawals twofold to the unacceptable adverse events and insufficient treatment efficacy. The results indicate that the combination therapy is also more tolerable but has a better symptom management, which leads to less patient dissatisfaction and treatment fatigue. Since compliance to topical therapy is a significant issue in scalp psoriasis, especially where the dosage is felt to be inefficient or aggravating, the reduction in the withdrawal rate is clinically significant. The increased treatment adherence is likely to result in increased disease control and patient quality of life (19). Adverse drug reactions were also generally reduced with the two-compound formulation as compared to all time periods that were considered. The common local reactions like pruritus, erythema, burning sensation, and skin irritation were less common than calcipotriol monotherapy. The interest of this finding is that vitamin D analogues are also known to cause local irritation in certain patients and this could be the limiting factor of tolerability in case of using the vitamin D analogues alone. These local inflammatory reactions seem to be suppressed by the addition of a corticosteroid, which leads to increased tolerability. Notably, the increased ADR rates under a two-compound preparation was not lost with both short and long-term exposure, which points to the applicability of the compound preparation in the long run. The fear of the long-term topical corticosteroid use, in particular, on the scalp, usually revolves around the possibility of local side effects, including skin atrophy, folliculitis, acneiform eruption, and ocular complications (20). In this study, the adverse events that were thought as potentially related to corticosteroid exposure were rare and were equally simple in both groups of treatment. The lack of a statistically significant difference in the number of overall corticosteroid-related events in the two-compound group is encouraging and indicates that the formulation provides the opportunity to control the disease effectively without the risk of the steroid-related risk, used as prescribed. The fact that serious or irreversible complications of corticosteroid use are very rare also proves the long-term safety of the combination therapy. The positive effects of safety of the present study can be explained by the additive effects of both calcipotriol and betamethasone dipropionate. Although calcipotriol regulates keratinocyte growth and differentiation, betamethasone has immediate anti-inflammatory properties, which used in combination allows successful management of the disease at a potentially reduced corticosteroid dose (21). The single-dose regimen of applications was also a contributing factor to higher-adherence and a decrease in irritation experienced with repeated applications, which occurred frequently with separate monotherapies. These findings have a number of limitations that should be taken into consideration when interpreting them. The trial was mainly concerned with safety and tolerability, and despite the fact that efficacy-related withdrawals were also evaluated, there were no specific endpoints of efficacy, and the objective of the analysis was not thorough. Moreover, although the duration of study provided meaningful assessment of the safety over time, post-marketing surveillance is still significant so as to identify the uncommon events of adverse events that may not be identified during clinical trials (22). Nevertheless, the high number of participants and long follow-up increases the credibility of the safety inferences. This research shows that the use of the two-compound calcipotriol and betamethasone dipropionate scalp formulation on a long-term and as-needed basis is linked to reduced withdrawal rates, reduced adverse drug reactions, and no rise in corticosteroid-related safety issues than that of calcipotriol monopharmacy (23). These results justify clinical application of the two-compound formulation as a safe and well-tolerated long-term management agent to treat scalp psoriasis because of its clinical and patient-related outcomes, including clinical efficacy and treatment compliance.

Conclusion

This randomized comparative study, which has a long duration and is randomized, is very robust in demonstrating the safety and tolerability of the two-compound scalp formulation containing calcipotriol and betamethasone dipropionate in the long-term management of scalp psoriasis under situations that are closely simulative to the conditions of real-life clinical practice. The assessment of long-term safety outcomes is particularly clinically critical considering the chronic and recurring nature of the scalp psoriasis disease and the most frequent need to have protracted or repeated topical solutions. The results of this study are relevant to fill an urgent gap because they prove that patient safety does not have to be sacrificed in the case of effective long-term disease control. In a large and well-balanced group of study participants, the two-compound formulation was more favorable in terms of safety than calcipotriol monotherapy. Combination therapy resulted in fewer adverse drug reactions in patients, as well as fewer common local reactions, including pruritus, erythema, burning sensation and skin irritation. Such tolerability changes were observed in the short term and long-term therapy thereby highlighting how the two-compound formulation is applicable in the long term. Notably, the decrease in the number of adverse reactions was followed by a substantial decrease in the rate of treatment discontinuation, which implies that the patients became more accepting and committed to treatment. One of the problems that are linked with the long term use of topical corticosteroid therapies is the possibility of corticosteroid side effects especially to the scalp where the absorption could be more effective. In this trial, the adverse events that were deemed as potentially related to corticosteroid exposure were not common but happened at equally low rates in both groups of the study. The two-compound formulation did not produce any clinically significant difference in corticosteroid-related events and the serious corticosteroid-related complications were infrequent. These results are a relief demonstrating that the regulated incorporation of a corticosteroid in fixed-dose combination does not reflect to higher safety risks in the long term when utilized in a proper manner. The positive results noted in this study may be accredited to the synergistic pharmacologic effect of calcipotriol and betamethasone dipropionate. The combination of antiproliferative and differentiation-normalizing action of calcipotriol and rapid anti-inflammatory activity of betamethasone is essential to ensure the effective management of the disease and, possibly, to reduce corticosteroid exposure. The once-daily application regimen also makes the process of treatment much easier and could lead to the enhancement of the treatment adherence rate which is a vital aspect of successful long-term scalp psoriasis management. Although the research was mainly on safety and acceptability, the found withdrawals as a result of inadequate efficacy, indicates that the two-compound formulation also provides a significant clinical effect. However, additional research that considers detailed efficacy endpoints and patient-reported outcomes can give more information on the long-term therapeutic benefits of this method.

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