Prospective, Observational, Non-Interventional, Multicentre Study on the Efficacy and Tolerability of a New Calcipotriol/Betamethasone Aerosol Foam (Enstilar®) in Patients with Plaque Psoriasis under Daily Practice Conditions

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Keywords

Quality of life · Real-world evidence · Topical therapy · Fixed combination

The new Cal/BD foam showed a convincing efficacy and tolerability profile in daily practice, particularly in patients with severer disease manifestations.

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Abstract

Background/Aims: To assess the efficacy and tolerability of the new aerosol foam of calcipotriol 50 µg/g plus betamethasone dipropionate 0.5 mg/g (Cal/BD foam, Enstilar®) in psoriasis vulgaris under daily practice conditions. **Methods:** 410 adult psoriasis patients (56% male) from 87 German sites were enrolled in a 4-week, open-label, prospective, non-controlled, observational, non-interventional study. **Results:** At baseline, patients presented with a psoriasis severity of mild (41.81%), moderate (49.63%), and severe (8.31%) assessed by an investigator global assessment (IGA). After 4 weeks of treatment, 49% of the patients achieved an IGA of clear/almost clear. The mean affected body surface area was reduced from 12.91 to 7.55%, the PASI from 10.4 to 5.2 ($p < 0.0001$). 43% of the patients with severe IGA achieved treatment success (IGA = 0/1 and ≥ 2 -step improvement). 93% of the patients did not show any adverse events. **Conclusion:**

Introduction

Psoriasis vulgaris (psoriasis) is one of the most common chronic inflammatory skin diseases in daily dermatological practice and is characterized by a chronic, episodic course. Quality of life is strongly impaired in affected patients [1–3]. According to the European S3 Guideline on the Therapy of Psoriasis Vulgaris [4], psoriasis is categorized into mild and moderate-to-severe forms. This categorization determines treatment decisions. The parameters used in clinical routine to assess disease severity are the psoriasis area and severity index (PASI), the investigator global assessment (IGA), the affected body surface area (BSA) and the dermatology life quality index (DLQI). The aim of a newly initiated treatment is a significant reduction of the PASI (at least a re-

Fig. 1. Study design: open-label, prospective, multicentre, observational, single-arm, non-interventional study in 87 German dermatological private practices and outpatient clinics. When calculating absolute, relative, and adjusted frequencies, patients with missing details were excluded. ITT, intention to treat.

duction of 50%) as well as an improvement in quality of life within 4–6 months. From the patient's perspective, an effective reduction of pruritus and confidence in their therapy is of importance, too [5].

Topical vitamin D₃ analogues and their fixed-dose combinations with topical corticosteroids are recommended as standard treatment for the induction therapy of mild-to-moderate psoriasis in the German and European S3 Guidelines [4, 6]. Several prospective studies and a meta-analysis of the Cochrane Database showed that the fixed-dose combination of vitamin D₃ and corticosteroids is superior compared to the administration of either substance on its own [7, 8].

Recently an innovative formulation of an aerosol foam has been developed for the established fixed-dose combination of calcipotriol (Cal, 50 µg/g) and betamethasone dipropionate (BD, 0.5 mg/g) (hereafter "Cal/BD aerosol foam"), which has been approved for the treatment of adult patients with psoriasis vulgaris in Germany since May 2016. This new formulation allows a state of supersaturation of the active substances in the aerosol foam carrier [9], which leads to increased skin penetration resulting in an increased local bioavailability in the skin and improved efficacy in comparison to the ointment and gel formulation [10].

In the clinical study programme, the Cal/BD aerosol foam demonstrated a significantly higher efficacy with

faster onset of action and improved convenience of application compared to both single substances and to other combination formulations (ointment, gel) [11–15]. Moreover, a rapid relief in itching as well as in sleep loss caused by itching in affected patients was observed.

This pilot non-interventional observational study aims to investigate the efficacy and tolerability of the new Cal/BD aerosol foam in a representative patient population in daily medical practice. Furthermore, the patient profile selected for this new therapy in daily medical practice will be described.

Method

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000486700 for all online suppl. material) [16] (Fig. 1).

Results

Patient Characteristics and Sociodemographics

Between August 2016 and March 2017, a total of 410 patients were enrolled at 87 German sites. The mean duration of observation was 4.55 ± 1.63 weeks. Of the in-

Table 1. Patient characteristics and sociodemographic data at inclusion (*n* = 410)

<i>Sociodemographic characteristics</i>	
Mean age $\pm$ SD, years	52.84 $\pm$ 15.33
Gender: male, %	56.10
Marital status: single/married/widowed, %	22.79/66.67/5.39
Education: secondary school/high school certificate/tertiary, %	64.23/17.13/16.37
Occupation: working or studying/unemployed or inability/retired, %	64.55/3.18/26.64
<i>Psoriasis medical history</i>	
Mean duration of psoriasis $\pm$ SD, years	15.34 $\pm$ 14.22
Previous therapy with topical drugs ^a , %	80.24
Topical corticosteroids	70.49
Vitamin D ₃ analogues	36.10
Previous therapy with systemic drugs ^a , %	15.61
Fumaric acid ester	9.51
Methotrexate	5.85
Apremilast	0.49
Biologicals	1.22
No previous therapy, %	17.32
<i>Comorbidities^b, total, %</i>	
Hypertension	23.17
Obesity	8.05
Coronary heart disease	6.34
Diabetes	5.85
Depression	4.63

SD, standard deviation. ^a Multiple answers possible. ^b By preferred term of the Medical Dictionary for Regulatory Activities (MedDRA 19.1).

cluded patients, 56% were male and 44% were female, with a mean age of 52.84 ($\pm$ 15.33) years. Patients presented with a mean duration of disease of 15.34 ($\pm$ 14.22) years (Table 1).

The severity of psoriasis (IGA, patient global assessment PaGA, BSA, and PASI) at inclusion is shown in Figure 2a–d. 31.98% of patients had a PASI >10 and thus a moderate-to-severe form. In 10.72% of patients even more than 30% of the BSA was affected.

80.24% of patients had been treated with a topical treatment before inclusion, primarily with corticosteroids and vitamin D₃ analogues. 15.61% of patients had recently received a systemic therapy, primarily with fumaric acid esters and methotrexate. 17.32% of included patients were treatment-naïve for any specific psoriasis therapy before enrolment (Table 1). 37.32% of patients presented with concomitant diseases, primarily arterial hypertension (23.17%), obesity (8.05%), coronary artery disease (6.34%), diabetes mellitus (5.85%), and depression (4.63%) (Table 1).

Assessment by Investigators

390 of the 410 patients included were assessed for efficacy by the investigators. 96.59% had applied the Cal/BD aerosol foam once daily. On average, 1.33 cans of the Cal/BD aerosol foam were opened during 4 weeks of treatment. In the majority of patients 1 can was sufficient (265 patients, 77.71%), and in 65 patients (19.06%) 2 cans were prescribed (Fig. 3). The comparison of the number of cans with the affected BSA at baseline and after 4 weeks of treatment (Fig. 3) showed a dose-dependent trend in the absolute reduction of affected BSA between the 2 groups (–4 vs. –8%). The groups of patients having used 3, 4, or more cans were too small (6 or 5 patients, respectively) for further analysis.

Concomitant topical treatment was applied in 18.05% of cases. 312 of 381 patients (81.89%) adhered to the Cal/BD aerosol foam therapy until the end of the 4-week observational period and were willing to continue the therapy thereafter. 57.65% of these patients continued a once-daily regimen, whereas the remaining patients reduced their application frequency with 18.24% of the patients using their treatment only “on-demand” and 23.76% of

Fig. 2. a–d Assessment of the severity of psoriasis at baseline according to investigator global assessment (IGA) (a), patient global assessment (PaGA) (b), body surface area (BSA) (c), and psoriasis area and severity index (PASI) (d).

Fig. 3. Number of Cal/BD aerosol cans used and according to body surface area (BSA) before and after 4 weeks of treatment with the Cal/BD aerosol foam ($n = 328$).

Fig. 4. Change in investigator global assessment (IGA) category before and after 4 weeks of treatment with Cal/BD aerosol foam. 49% reached a clear or almost clear IGA class ($n = 374$). The difference was statistically significant ($p < 0.001$, Bhapkar test).

the patients followed a fixed, but reduced dosing interval regimen. In 18.11% (69 out of 381 patients), treatment was withdrawn before or at the end of the 4-week observational period. The main reason for treatment discontinuation was “having achieved the treatment goal” (9.02%), whereas “insufficient response” appeared to be the reason in only 3.17% (Fig. 1).

After 4 weeks of treatment with the Cal/BD aerosol foam, a total of 49.47% of patients achieved complete or almost complete clearing of their lesions independently of how severe their psoriasis was at study entry (Fig. 4). The difference in severity in IGA between baseline and at week 4 was statistically significant ($p < 0.001$; Bhapkar’s test). In particular patients with an IGA of 4 (= severe psoriasis) at inclusion benefitted from the Cal/BD aerosol foam treatment: 43.33% achieved treatment success after 4 weeks of treatment, defined as being clear/ almost clear and a ≥ 2 -step improvement in the IGA, compared to 24.33% of the total population.

As shown in Figure 5a–c significant improvement in PASI, affected BSA as well as in IGA ($p < 0.0001$; Wilcoxon log-rank test) was observed after 4 weeks of Cal/BD aerosol foam therapy.

For the safety analysis, data from 391 patients from 87 sites were available. A total of 29 adverse events were documented in 28 patients (7.16%). No serious or severe adverse event was reported. The majority of adverse drug reactions (23 of 28 patients) were related to “non-efficacy”; all other adverse events occurred occasionally in isolated patients only (Table 2).

Overall, tolerability was assessed as very good or good by 98.94% of investigators (Fig. 9).

Table 2. Adverse events coded according to the preferred term in the Medical Dictionary for Regulatory Activities (MedDRA 19.1)

Reported adverse events	Patients, <i>n</i>	Frequency, %
Insufficient response	23	5.88
Diarrhoea	1	0.26
Increased blood glucose levels	1	0.26
Severe constipation	1	0.26
Itching at application area	1	0.26
Confusional state	1	0.26
Influenza-like symptoms	1	0.26

Assessment by Patients

A total of 391 patients documented psoriasis severity at inclusion in their patient diary (Fig. 2b). Attributes perceived immediately after the first application of Cal/BD aerosol foam are shown in Figure 6. 71.10% of patients assessed the aerosol foam as very/quite cooling, 66.47% as very/quite skin satisfying, and 59.39% as very/quite itch relieving. Application was considered as very/quite simple by 88.64%.

After 2 weeks, the patients were asked about the onset of relief of signs and symptoms of psoriasis. After 3 days 15.83% observed a first visible improvement of their signs of psoriasis, and 28.63% reported to have 24 h without itching; after 1 week this was observed in 67.74% and 60.25%, respectively (Fig. 7). Similarly, the weekly recorded symptom scores on itching, insomnia due to itching, xerosis, desquamation, and erythema improved as well (Fig. 8).

Fig. 5. a–d Mean change in different efficacy outcome parameters (BSA, IGA, PASI, and DLQI) after 4 weeks of treatment with the Cal/BD aerosol foam (mean, standard deviation, and median). All changes were statistically significant ($p < 0.0001$, Wilcoxon log-rank test).

Fig. 6. Immediate patient assessment of given attributes after the first use of the new Cal/BD aerosol foam according to a 4-point Likert scale. Patients with missing values were not included in the relevant analysis.

Fig. 7. Time to visible response in symptoms and reduction of itching assessed by patients reflects the fast onset of action of the Cal/BD aerosol foam.

Fig. 8. Improvement of the symptoms itching, sleep loss due to itching, xerosis, desquamation, and erythema measured with a 10-point scale (numerical rating scale) by patients on a weekly basis over time ($n = 382$ patients).

After having completed 4 weeks of treatment, 36.70% of patients estimated their psoriasis as clear/almost clear in the PaGA (compared to 0.80% at inclusion). 37.68% of patients showed a clinically significant relief in pruritus, defined as a reduction in the 10-point scale by at least 30%. 43.10% of patients stated that their psoriasis had no influence (DLQI = 0 or 1) on their quality of life (compared to 10.42% at inclusion). In the final assessment, 94.77% of patients were very satisfied or satisfied with the tolerability of the Cal/BD aerosol foam (Fig. 9).

Discussion

This investigation represents the first study on the efficacy and tolerability of Cal/BD aerosol foam in a representative German dermatological patient population un-

der daily practice conditions. A total of 49.47% of patients achieved a clear/almost clear status as per IGA; the mean reduction in affected BSA was 41.52%; the mean PASI reduction was 50% after only 4 weeks of Cal/BD aerosol foam therapy. Revealing a remarkable fast response, two thirds of patients perceived a notable or visible relief of their symptoms after only 1 week. The treatment was very well tolerated with 92.84% of patients not showing any adverse event within the 4-week observation period. In summary, these results confirm the high efficacy, rapid onset of action and good tolerability of the Cal/BD aerosol foam as known from randomized clinical trials (RCTs) also under daily practice conditions.

However, compared to the phase 3 trials there were significant differences in the characteristics of the included patient populations, in particular with regard to the severity of the disease and the amount of medication

Fig. 9. Assessment of satisfaction with the Cal/BD aerosol foam and previous treatment with regard to efficacy, tolerability, and handling by both investigators and patients.

used. The patients included in this study showed a mean affected BSA of 12.91% at inclusion, and compared to the RCTs their psoriasis was almost twice as extensive (BSA of 7.7 or 7.4%) [11, 12]. A similar difference was observed on the initial PASI score of 10.3 compared to 7.0 or 7.4 in the RCTs [11, 12]. On the other side the IGA of the severity in this study showed more often the category “mild” compared to the physician’s assessment in the clinical study program (41.81% compared to 15.6 or 15.5%) [11, 12], whereas the percentage of patients with severe psoriasis was comparable at 8%. Interestingly, the IGA of disease severity was not revealed in the PaGA, in which only 16% of patients categorized their psoriasis as mild and 27% as severe (Fig. 2). This is of importance, as apart from a reduction in the PASI, BSA and DLQI, the primary end point defined as “treatment success” also required a 2-step or more reduction in the IGA and explains why this goal was achieved less frequently in this study than in the clinical study program. As this definition of treatment success requires that mild to moderately assessed patients achieved complete clearance of their lesions, it must be discussed in the future whether this outcome parameter as defined per Langley et al. [16] is a suitable parameter for a patient population consisting of predominantly mild and moderate psoriasis by IGA, but where the more extensively affected BSA is not taken into consideration as well. Further correlation analysis to assess whether e.g. other composite tools, like IGA × BSA, for the assessment of disease severity are more suitable to assess burden on

patients than PASI or IGA alone in a more mild-to-moderate dominated psoriasis patient pool might be subject to future analysis [16, 17].

This is further supported by the fact that patients with “severe” psoriasis (as per IGA) in particular benefit from the Cal/BD aerosol foam therapy: 43.33% achieved treatment success (defined as clear/almost clear and at least 2-step improvement in the IGA), compared to 24.33% in the overall population. Symptoms such as pruritus and the affected BSA might influence the subjective perception of the disease in the PaGA more than it is reflected in the physician global assessment, whereas the PASI (including both severity assessment and BSA) reveals the patient’s assessment better than the IGA does (Fig. 2b, d).

Another reason for the discrepancy between the IGA and PASI might be that the IGA is not part of the consented treatment goals in psoriasis [18] and thus might be used less often in daily practice compared to the PASI for assessing severity of psoriasis in patients. The sites participating in this non-interventional study (NIS) were predominantly private practices and might be less familiar with scores like IGA compared to sites specialized in clinical studies.

Improvement in quality of life with a DLQI score of 0 or 1 was reported by 43.1% of patients after 4 weeks of therapy and was slightly lower compared to 48.1% reported in the PSO-FAST study. Both values, however, indicate a high proportion of patients with no impact on quality of life any more after a 4-week treatment with the Cal/BD

aerosol foam, whose quality of life had been heavily impacted by the disease before treatment (8.25 in this study vs. 10.42 in the PSO-FAST study).

Chronic pruritus is associated with an increased psychiatric comorbidity [19], sleep loss [20], and a considerable impact on quality of life [21–23]. The results of this study support the good and rapid efficacy of the Cal/BD aerosol foam on pruritus symptoms as well. The immediate perception of the foam formulation as “cooling” can be a possible explanation for the rapid onset of this effect.

In the RCTs at week 4, the mean total amount of Cal/BD foam used was 120.8 g in patients with a mean BSA of 7.4%. The total amount of Cal/BD foam was greater with increasing BSA [24]. In this NIS the quantitative assessment of the use of BD/Cal aerosol foam was measured in 341 patients after 4 weeks of treatment by the number of cans used (= opened). One BD/Cal can contains 60 g BD/Cal of aerosol foam, but the exact amount of BD/Cal aerosol foam remaining in the can at the end of the study was not measured. We could also show that the number of cans used in this NIS was greater with increasing BSA and that the absolute reduction of BSA increases with the number of cans used in a dose-dependent manner. Assuming that on average 1.33 cans used in this study would represent about 80 g of the Cal/BD aerosol foam and considering the fact that this was used in patients with a mean affected BSA of 12.91%, it shows that under daily practice conditions the amount of medication applied per affected BSA was more than 50% less of what has been applied in RCTs where the applied amount has been weekly measured and further outlines the efficacy of the new formulation in daily practice.

We could observe that under daily practice conditions, considerably more patients with a higher proportion of affected BSA and a higher PASI score were selected for the Cal/BD aerosol foam treatment compared to RCTs. The majority of these patients had previous experience with therapy, and 15.6% of those patients had already received systemic therapy before. Despite those exhausted therapies in the past, this study showed that a large proportion of the patients could still benefit from therapy with the Cal/BD aerosol foam, and “treatment failure” was reported in only 5.8% of patients for the Cal/BD aerosol foam.

Controversial discussion is required on the fact that in this NIS, which also aims to describe treatment behaviour in daily practice in Germany, 10.7% of patients with an affected BSA of >30% were enrolled, though this was defined as an exclusion criterion in the NIS and is mentioned in the summaries of product characteristics (SmPC) as the upper limit of BSA, on which the Cal/BD

aerosol foam should be applied. Though these patients did not report any side effects, patients with such an extensive disease are known to have a high intrinsic inflammatory burden and should receive systemic therapy as recommended in guidelines. A topical therapy in this case can only temporarily serve for the relief of the skin symptoms and might have only be initiated to bridge the patient’s time until initiation of the next systemic therapy.

Further data are needed to assess the long-term effect of the Cal/BD aerosol foam under daily practice conditions, as well as to show whether the achieved response can be maintained beyond week 4 of the observation period – in particular in those more severely affected patients for whom initially a particular good response rate was observed. A phase 4 study (PSO-REAL) is currently ongoing for those purposes.

Conclusion

In conclusion, results from this first study under daily practice conditions confirm the high efficacy, rapid onset of action, effective reduction of pruritus and good tolerability of the new Cal/BD aerosol foam as observed in clinical studies. Due to the considerable number of moderate-to-severe psoriasis patients (according to the affected BSA), it could be shown that these types of patients can benefit from using the Cal/BD aerosol foam, too. Acceptance of the foam formulation was high, and the application was perceived as very/quite simple by the majority of patients.

Key Message

Daily practice experience confirms the high efficacy and tolerability of the Cal/BD foam, also in moderate-to-severe plaque psoriasis.

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Statement of Ethics

The patients provided a written informed consent for the use of their data in this study.

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