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TREATMENT OF PSORIASIS VULGARIS WITH CALCIPOTRIOL BETAMETHASONE DIPROPIONATE COMBINATION FOLLOWED BY CALCIPOTRIOL AND ASSESSMENT OF THE ADJUVANT BASIC USE OF UREA-BASED EMOLLIENTS

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A new combination product containing betamethasone dipropionate and calcipotriol (Dovobet® ointment) has been proven very effective and well tolerated in patients with psoriasis vulgaris. Emollients are adjunctive modalities commonly used in psoriasis; however, their actual role in combination with topical drugs as well as well as their compatibility with these drugs have not been well elucidated. In 313 adult patients with psoriasis vulgaris, we studied the efficacy and tolerability of treatment with Dovobet® ointment combined with urea-based emollients (Excipial U®) for 4 weeks, followed by treatment with calcipotriol (Daivonex®) either alone (group A) or combined with urea-containing emollients (Excipial U®, group B) for 8 weeks. Clinical evaluations were performed at baseline, at 4 and 12 weeks, assessing the clinical score for erythema, scaling, infiltration and pruritus, graded on the basis of a 5-point scale. After the initial 4-week treatment, a significant improvement of all clinical parameters was observed ($p<0.05$). Overall, clinical results improved further during the maintenance treatment phase; significant changes ($p<0.05$) were observed in each group. Most patients considered treatment efficacy positively at both 4 weeks and 12 weeks. Interestingly, at the end of the study, a greater percentage of patients in group B than in group A judged the efficacy as excellent. Treatment was very well tolerated. Only two patients complained of mild and transient burning sensation during the first days of treatment. The results of this study confirm the great efficacy and tolerability of sequential treatment with Dovobet®, and Daivonex® in psoriasis vulgaris and show the enhanced acceptability of this treatment associated with urea-based emollients.

Corticosteroids and calcipotriol, a synthetic analogue of 1,25-dihydroxyvitamin D3, are widely used topical treatments for psoriasis and have been used separately for many years to treat this skin disorder. Both corticosteroids and calcipotriol affect at variable degree inflammatory processes and keratinocyte differentiation and proliferation, but their mechanisms of action are quite different (1-4).

Key words: psoriasis vulgaris, calcipotriol, betamethasone dipropionate, combination product, emollients, urea.

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Dovobet® ointment is a new combination product containing 0.5 mg/g betamethasone dipropionate and 50 microg/g calcipotriol. Clinical studies have shown that the combination product has greater efficacy and tolerability and a faster speed of onset than either agent used alone (5-10). It is usually administered once daily for up 4 weeks followed by maintenance treatments with steroid-free conventional products (e.g., calcipotriol alone).

Emollients are important adjunctive therapeutic modalities in various skin disorders (11,12), such as psoriasis; however, despite their frequent use, there are only scanty reports evaluating the actual adjuvant role of emollients combined with topical drugs as well as their compatibility with these drugs.

Among emollients, the beneficial role of urea has been well recognized for a long time and has been demonstrated in several skin disorders, including atopic dermatitis and psoriasis (12-17). Its value has been proven in clinical trials to be compatible with other topical therapies and biocompatible with the skin, thus fulfilling the criteria for the definition of "therapeutic moisturizers" proposed by Bikowski (11).

The aim of this study, performed in patients with psoriasis vulgaris, was to evaluate the efficacy and tolerability of treatment with Dovobet® ointment combined with urea-containing emollients (Excipial U®) for 4 weeks, and, in the subsequent 8-week maintenance phase, the efficacy and tolerability of Daivonex® either alone or combined with Excipial U®.

MATERIAL AND METHODS

This was a multicentre open study which was carried out from December 2003 to May 2004 in adult patients with psoriasis vulgaris. Patients with guttate, erythrodermic, exfoliative, arthropathic or pustular psoriasis and other inflammatory skin conditions were not included. Also excluded was the use of systemic active treatment, phototherapy or sun exposure 6 weeks before or during the study, topical treatment with either antipsoriatic drugs or emollients/keratolytics 2 weeks before or during the study. Other exclusion criteria were: use of drugs apt to influence psoriasis; relevant concomitant diseases which could have required prohibited treatments; any known contraindications to the use of study products; pregnancy and breast-feeding.

Patients underwent a 12-week treatment regimen, consisting of two sequential phases.

In the initial 4-week phase, all patients applied Excipial U® Hydrolotion (containing 2% urea in an o/w formulation, 11% fat content) once daily (o.d.), in the morning, and Dovobet® ointment o.d., in the evening. At 4 weeks, patients entered an 8-week maintenance phase. They were sequentially allocated, according to 1:1 ratio, to one of the following treatment groups:

- Group A: Daivonex® cream o.d., in the morning, and Daivonex® ointment, o.d., in the evening;
- Group B: the same regimen of group A combined with urea-based emollients: patients were instructed to use Excipial U® Hydrolotion o.d., in the morning, and Excipial U® Lipolotion (with 4% urea in a w/o formulation, 42% fat content) o.d., in the evening.

Clinical evaluations were performed at baseline (day 0), at 4 weeks and at the end of the study (12th week), assessing the clinical score for erythema, scaling, infiltration and pruritus, graded on the basis of a 0-4 scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe).

As for the statistical analysis, the one-sample Kolmogorov-Smirnov test did not show a normal distribution of the baseline clinical parameters. Therefore, the changes of clinical scores were evaluated with a non-parametric test (Wilcoxon matched-pairs signed-ranks test). The analysis of the two groups in the maintenance phase was made using two-sample Kolmogorov-Smirnov for comparison of symptom scores. In all analyses, significant differences corresponded to p values <0.05. At the end of the initial phase, both patients and physicians gave their judgement on the overall efficacy; thereafter, the same assessment was performed by the patients at the end of the 12th week study period. Tolerability was assessed by recording any adverse events; these were also adequately monitored.

RESULTS

After obtaining an oral informed consent, 313 patients, 172 women and 141 men (mean age, 44 years), were recruited. The most affected skin areas were upper limbs (240 cases) and lower limbs (233 cases); involvement of the head and trunk was detected in 96 and 73 patients, respectively. At the baseline, most patients (72%) complained of pruritus of variable intensity.

All patients were evaluated after the initial 4-week treatment, which caused a significant improvement of

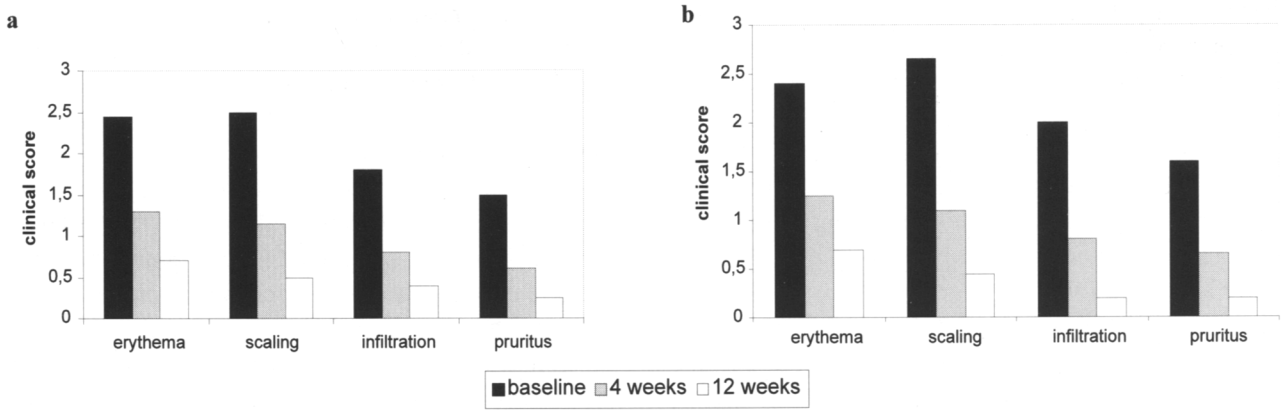

Figure 1. *Change of clinical score of signs and symptoms throughout the 12-week study period. Response in group A (a) and in group B (b).*
Week 4 vs baseline: $p<0.05$ for all parameters in each group
Week 12 vs Week 4; Week 12 vs baseline: $p<0.05$ for all parameters in each group

all clinical parameters ($p<0.05$). Thirty-two patients dropped out from the study before the final visit; most of them (22 cases) were lost to follow-up. Other reasons for premature discontinuation were: complete clearance of lesions (6 patients), inefficacy (2 patients), and poor compliance (2 patients). Therefore, 281 patients completed the trial protocol, 140 in the treatment group A and 141 in group B. After the maintenance treatment phase, scores of all clinical items further improved and statistically significant changes ($p<0.05$) were observed in each group. There was a tendency towards a greater reduction of infiltration in group B, but this difference did not reach the level of significance. Figure 1 shows the clinical score in both treatment groups throughout the 12-week study period. The efficacy of treatment was considered positive by most patients and physicians at both 4 weeks and 12 weeks (Tab. I). A greater percentage of patients in group B (47%) than in group A (33%) judged the efficacy as excellent. Treatment was very well tolerated. Only two local adverse reactions (0.6%) were observed, consisting of mild burning sensation, which developed in both cases within the first days of treatment and faded away spontaneously after 2-4 days.

DISCUSSION

The results of our study confirmed the high efficacy and tolerability of treatment with Dovobet® ointment in psoriasis vulgaris. Thanks to an innovative formulation, this product preserves the activity and bioavailability of the active components which otherwise are incompatible for simultaneous application

Table I. *Opinion on treatments efficacy over the study period.*

	Absent	Poor	Discrete	Good	Excellent
4 WEEKS (313 cases)					
Patients opinion (%)	0.5	4.5	12	55	28
Investigators opinion (%)	0	3	14	57	26
12 WEEKS (281 cases)					
Patients opinion (%) ø Group A	0	2	10	55	33
Patients opinion (%) ø Group B	0	2	7	44	47

because of pH stability problems (18). The simultaneous application of two drugs with different and synergistic mechanisms of action can explain the superior efficacy of the combination product as compared to monotherapy with each drug (19,20). Treatment with the combination ointment gives relevant advantages also in terms of patient's compliance, thanks to the once-daily application, quality of life parameters and tolerability profile (5-10). The use of combination product may reduce the risk of adverse events associated with the long-term use of corticosteroid monotherapy (atrophy and rebound) as well as the irritation associated with calcipotriol (18,21,22).

In our study population, the results obtained after the initial phase with Dovobet® could be maintained or further improved with treatment with Daivonex® alone, as shown by previous studies (7,9).

Emollients are commonly used in various chronic skin barrier disorders (11,12,23), in which they offer multiple potential benefits: improvement of skin hydration and barrier function, reduced susceptibility to irritants, enhanced penetration of active ingredients, decrease of inflammation and itch and subsequent steroid-sparing effects. However, in clinical practice, the effects of emollient preparations are quite different and largely dependent on the type and concentration of moisturizing substance, and the formulation and ingredients of the manufactured products. Urea is a physiological substance with moisturizing and water-binding properties, as well as other multifunctional effects: restoration of skin barrier functions with decreased transepidermal water loss and reduced susceptibility to irritants and infections, enhancement of penetration of active ingredients, antipruriginous and antimicrobial effects (12-17). Moreover, it has been shown that topical treatment with urea directly influences keratinocyte proliferation and differentiation in psoriasis (24).

In our study, the addition of urea-based emollients Excipial U® to both Dovobet® ointment and Daivonex® was well tolerated and accepted by patients. Interestingly, a greater percentage of patients in group B (Daivonex® + Excipial) gave very positive judgements of treatment efficacy as compared with patients in group A (Daivonex® monotherapy). In fact, patients in group B rated the efficacy as excellent more frequently than patients in group A (47% versus 33%), indicating that the addition of emollients increased the self-perceived effectiveness and acceptability of treatment. These results might also have positive consequences on the patient's compliance and adherence, which are of crucial importance for the management of chronic skin diseases affecting patient's quality of life, such as psoriasis (25,26).

Our results demonstrate that adjuvant basic treatment with the emollients evaluated in this study is compatible with the use of either calcipotriol/betamethasone dipropionate or calcipotriol in psoriasis vulgaris, suggesting the role of the these emollients as 'therapeutic moisturizers' (11), and seems to augment the patients' self-perceived efficacy and acceptability of pharmacologic treatment.

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