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ORIGINAL PAPER

Validation of Dermaphot® for the assessment of steroid-induced skin atrophy

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Abstract Currently, there are no accurate and simple methods available to measure this risk of atrophy in patients treated with topical glucocorticosteroids. In the present clinical trial, we validated a new score (Dermaphot® score) to assess the atrophogenic potential of glucocorticosteroids. 36 healthy adult volunteers were included in an investigator-initiated, blinded, randomized, intra-individual comparison, vehicle controlled multi-centre study. Subjects were treated in a randomized manner for 3 weeks with pimecrolimus cream 1 %, mometasone furoate (1 mg/g), clobetasol propionate 0.05 % and vehicle. In addition, ultrasound examination for skin thickness was performed. Data demonstrated a direct correlation of the achieved Dermaphot® score and the ultrasound thickness measurements. Our study shows that the Dermaphot® score can be used as a simple method to evaluate the atrophogenic potential of glucocorticosteroids. Respectively, we showed that the new score is an easy, valid and sensitive new tool for early detecting and quantifying even subclinical glucocorticosteroid-induced skin damage. We demonstrated that the score is able to differentiate the extent of skin atrophy (damage) after 3 weeks of topical glucocorticosteroid application with different levels of skin transparency and levels of telangiectasia.

Keywords Dermaphot® score · Atrophy · Telangiectasia

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Introduction

Glucocorticosteroid (GC)-induced skin atrophy limits the long-term use of topical GCs in the treatment of atopic eczema [3, 7]. The typical sign of such skin damage is skin atrophy reflected in an increased transparency and shininess of the skin probably caused by decreased fibroblast growth and reduced synthesis of collagen and acid mucopolysaccharides [12]. Another indicative sign of GC-induced skin damage is telangiectasia characterized by an abnormal dilatation of capillary vessels and neo-vascularization of arterioles which is a consequence of stimulation of human dermal microvascular endothelial cells. GC damage appears also as striae, which are visible linear scars in areas of dermal damage probably also due to the disturbed collagen metabolism by steroids [10]. GC-induced purpura comprises scars which present with a purpuric colour and hypopigmentation as a consequence of GC-induced loss of intercellular substance leading to loss of the dermal matrix surrounding blood vessels. Irrespective of purpura, other pigmentary changes can also occur after topical GC treatment [5]. Previous studies have also demonstrated an increase in transepidermal water loss with topical GCs which has been related to a damage of the skin

barrier function of the stratum corneum as a consequence of a GC-induced reduction of the density of corneodesmosomes in the lower stratum corneum [6].

According to clinical experience the reversibility of these skin changes is inversely related to their severity, treatment duration and topical GC strength. However, it is often difficult to detect early signs of GC-induced skin damage with the naked eye. A wide variety of non-invasive methods have been developed in recent times to assess GC-induced skin atrophy in the last years [5]. Those include vasoconstriction assays, confocal laser scanning or measurements of the skin thickness using micrometer screw gauges [11]. Another common technique for measuring skin atrophy and skin thickness is ultrasound. However, this method as the previous ones requests specific equipment, is time consuming, and is associated with the risk of methodological bias. Recently, a new method for detection of clinically unapparent steroid damage of the skin by dermoscopic assessment has been described in the literature [2, 14, 15].

The aim of the current study was to use this new assessment technique to establish and validate a new score for skin atrophy and telangiectasia (Table 1) which is able to differentiate the extent of skin atrophy (damage) after 3 weeks of topical steroid application with different atrophogenic potency and compare it to non-atrophogenic anti-inflammatory formulations and vehicle.

Patients and methods

Study ethics and design

This was a 5-week investigator-initiated, investigator-blinded, randomized, intra-individual comparison, vehicle controlled multi-centre study, including a treatment period of 3 weeks and a 2-week follow-up period. The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki at three study centres. The ethics committee of each centre reviewed the protocol and granted approval prior to study initiation. The study design was explained to the healthy volunteers who were capable of understanding the purposes and risks of the trial, and written informed consent was obtained from each of the volunteers before study enrolment. The study consisted of a 3-week treatment phase followed by a 2-week follow-up period. The study was registered under the EudraCT number 2007-006272-11 at the database of the European Medical Agency (EMA).

Table 1 Overview of the definition of Dermaphot® scores used for the examination of (A) skin transparency and (B) telangiectasia

Score	Definition
(A) Skin transparency assessment (range 0–4)	
0	No change
1	Slight transparency increase
2	Moderate thinning of the epidermis with moderate increase in transparency
3	Severe thinning and increase in transparency
4	Very severe thinning of the epidermis, the vasculature appearing to be directly under the surface
(B) Telangiectasia (range 0–4)	
0	Normal vascular pattern
1	Capillary hyperaemia with slight elongation and dilatation of blood vessels not visible to the naked eye
2	Moderate telangiectasia, just visible with the naked eye
3	Severe telangiectasia
4	Very severe telangiectasia with large blunt vessels

Study population

The study population consisted of 36 adult healthy volunteers (18–60 years of age) with no signs of skin atrophy in the investigated areas of the lower forearms. All volunteers were free of any clinical conditions that according to the investigator may have interfered with the Dermaphot® evaluation (e.g. generalized erythroderma, the genetic condition Netherton's syndrome or other skin conditions such as atopic dermatitis, psoriasis). Beyond that, the volunteers showed no history of malignancies of any organ systems, no clinical signs of infections in the treatment area and no history of hypersensitivity to the ingredients of the investigated topical creams. Patients were excluded if they were pregnant or nursing (lactating) women. Also, females of childbearing potential and not practicing a medically approved method of contraception during and up to at least 4 weeks after the end of treatment were excluded to participate in the study. Subjects were also not allowed to participate in the trial in case of the use of other investigational drugs within 30 days prior to enrolment.

Randomization and blinding

At visit 1, all subjects were assigned a unique subject number by the investigator. The subject number contained two parts: the first part indicated the centre number, which was assigned by the coordinating investigator site (Frankfurt/Main). The second part contained the lowest available number from the consecutive numbers allocated to the study site.

The subjects applied all investigational and control drugs at the same time using a within-patient design. Each volunteer received a randomized package with study medication according to the previously subscribed screening number. Study medication was labelled A–D in a randomized manner, e.g. subject 01–01 received pimecrolimus in tube A, subject 01–02 received pimecrolimus

in tube B. Volunteers applied the study medication twice daily in distinct treatment areas identified by personalized transparent pattern sheets for the left and right forearm (as shown in online resource 1). Study drug application was unblinded for the volunteers. At the study visits, treated areas were assessed by blinded investigators for Dermaphot® assessment and ultrasound measurement. All assessments were performed by the same investigator for all subjects of a site to exclude intra-individual errors in the scores.

Study treatment and safety assessments

Study treatments [pimecrolimus 1 % cream, mometasone furoate 1 mg/g, clobetasol propionate 0.05 % and vehicle (essex® basecream)] were commercially available products labelled for clinical study use according to German law by local pharmacies. Adjustments to the daily application frequency of investigating drugs (i.e. change from BID to OD) were not permitted during this study. As a general principle, additional treatments which could influence the skin thickness evaluation had to be discontinued prior to the study start and were omitted during the study period. The study treatment was discontinued for a given subject if the investigator determines that continuing it would result in a significant local safety risk, e.g. atrophy, for that subject.

Volunteers were evaluated at each study visit for safety. Any adverse events identified in the time course of the study including the safety follow-up visit were recorded.

Clinical assessments

The Dermaphot® assessments were performed at each visit on the marked and treated medial aspect of both upper arms. Both lesional and peri-lesional skin were evaluated by means of the handheld dermoscope (Delta 10 or 20; Heine Optotechnik, Herrrsching, Germany), with a fixed magnification ×10; and photographed with Dermaphot® photographic equipment (Heine Optotechnik). Skin atrophy and telangiectasia was assessed using the Dermaphot® score—a modified Frosch score [4] (Table 1). All participating investigators were trained on Dermaphot® assessments and the scoring prior to initiation of the trial or had previous experience with the scoring system.

At selected sites the skin thickness of the primary target lesion areas was additionally evaluated at all visits by ultrasound using a 20–25 MHz transducer coupled with an ultrasound device (e.g. Cortex Technology, Hadsund, Denmark). The assessments of skin thickness were performed by outlining the image of the whole skin block on the screen [1, 13].

Statistical analysis

In this study, four treatment groups were compared pairwise. The sample size for this study was based on the following assumptions: (1) clinically significant difference: 1.2 points, (2) standard deviation in each group: 1.2 points, (3) alpha error (two-sided): 5 %, and (4) beta error: 10 % (90 % power). Based on these assumptions a sample size of 30 was calculated. To compensate for drop outs 36 patients were recruited into the study.

Data are expressed with SE. All P values are two-tailed, and values of $p < 0.05$ were considered to indicate statistical significance. The Wilcoxon ranking test for matched pairs was used for statistical analysis.

Results

A total of 36 healthy volunteers with no signs of atopic dermatitis were enrolled into this investigator-blinded, randomized, intra-individual vehicle controlled multi-centre study. Overall, 24 female (66.6 %) and 12 male (33.3 %) volunteers with a mean age of 33 (range 19–57 years) participated in the clinical trial. The mean demographic characteristics were similar between all recruiting sites (Table 2). Subjects had to participate at five visits during the trial after the informed consent was obtained at visit 1. At this visit patients were randomized according to their subject number and received a study medication kit containing pimecrolimus 1 % cream, mometasone furoate (1 mg/g), clobetasol propionate 0.05 % and vehicle. According to the study protocol, subjects applied the different study medications twice daily in distinct treatment areas on the left and right forearm on previously determined areas (refer to online resource 1). To identify the treatment areas for all visits, nevi or vessels were marked on the transparent sheets of each volunteer to position the pattern sheet accordingly.

Table 2 Demographic data of the 36 volunteers participating in the clinical trial

	Gender	Mean age (years)	Mean height (cm)	Mean weight (kg)
Overall ($n = 36$)	24 f/12 m	33.0 ± 9.9	172.2 ± 9.6	68.5 ± 11.3
Frankfurt ($n = 12$)	8 f/4 m	29.3 ± 8.6	170.7 ± 7.4	65.0 ± 9.5
Münster ($n = 12$)	9 f/3 m	35.8 ± 10.7	175.5 ± 9.9	71.3 ± 10.3
Dresden ($n = 12$)	7 f/5 m	34.2 ± 9.9	168.6 ± 8.6	66.0 ± 12.0

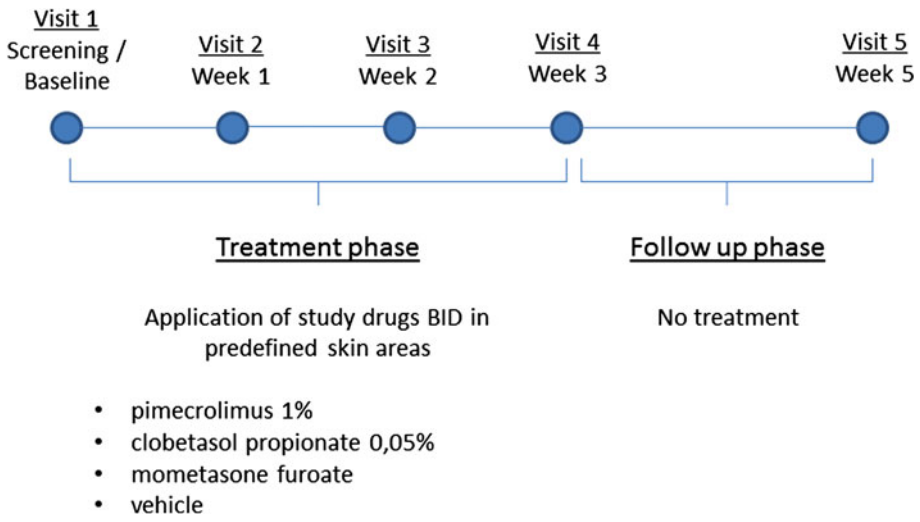

Fig. 1 Scheme of study design and visit schedule

As shown in the visit assessment schedule in Fig. 1, the study-specific dermoscopic measurement and ultrasound measurement were obtained at all visits excluding visit 5 which was performed as a safety follow-up visit 2 weeks after the last treatment with the topical study ointments. Dermoscopic and ultrasound assessments were performed for all 12 volunteers per site throughout the trial by the same blinded investigator to ensure that data were acquired consistently. At the baseline visit the dermoscopic assessment showed that there were no significant differences in the Dermaphot® score of the four different skin treatment areas. The Dermaphot® score was in a range between 0.30 and 0.39. Already 1 week after the start of the treatment the dermoscopic measurements indicated a tendency of an increase of the Dermaphot® score in the areas treated with the topical steroids in comparison to pimecrolimus 1 % and vehicle cream. This tendency was confirmed by the assessments which were done after 2 and 3 weeks of treatment. A significant increase ($p < 0.05$) of the Dermaphot® score values could be measured for the skin areas treated with the super-potent topical steroid clobetasol propionate 0.05 % (WHO class I). The Dermaphot® value was 2.20 in contrast to 0.55 for the vehicle control or 0.57 for pimecrolimus 1 % cream. The Dermaphot® score of the mid-potent topical steroid mometasone furoate (WHO class III) was 1.21. In comparison with the baseline values of the vehicle-treated skin area, the Dermaphot® score of clobetasol propionate was significantly increased at week 2 and further on at week 3. At week 3 the Dermaphot® score of clobetasol propionate was also significantly increased compared to pimecrolimus 1 % cream. Also, the mometasone furoate (1 mg/g) value at week 3 was significantly increased compared to the baseline value. No significant difference was detected between the vehicle and pimecrolimus 1 % cream (Fig. 2a). Dermaphot® score showed an increase of 7.48-fold at week 3 compared to baseline for the clobetasol propionate. Mometasone furoate (1 mg/g) was increased by 2.25-fold at week 3. Both values were significantly increased compared to the baseline values of the vehicle. In contrast, vehicle and pimecrolimus 1 % cream showed a non-significant increase of 0.64 and 0.57 fold (Fig. 2b).

The analysis of the Dermaphot® score was done by analysing the Dermaphot® pictures. A sample Dermaphot® picture series of one subject is shown in online resource 2. Telangiectasia and skin atrophy are visible on the close-up Dermaphot® pictures after 2 and 3 weeks of treatment with clobetasol propionate and mometasone furoate. In contrast, pimecrolimus 1 % cream and vehicle cream-treated areas showed no induction of telangiectasia and skin transparency over the time of treatment.

To validate the Dermaphot® score values, the assigned treated skin areas of the 36 volunteers were additionally examined using ultrasound. As shown in Fig. 3 ultrasound measurements highlighted a significant decrease in skin thickness after 3 weeks of treatment in the skin areas treated with topical steroids. At week 0 the mean skin thickness was 1,014 µm. Already after 1 week areas treated with clobetasol propionate showed a decrease of skin thickness of −10.7 % (894 µm). At week 3 the decrease of skin thickness in the steroid treated areas was about −18.5 % (826 µm) for clobetasol propionate and −13.8 % (874 µm) for mometasone furoate. Areas treated with non-steroid cream showed no significant reduction of skin thickness (−2.1 %; 993 µm).

All 36 subjects completed the study. One subject discontinued treatment with clobetasol propionate after 14 days due to an increased risk to develop visible skin atrophy in the treated skin area. The most common adverse events reported were headache (2 cases) and hypopigmentation (2 cases). In total, 7 different adverse events (headache, hypopigmentation, common cold, erythema,

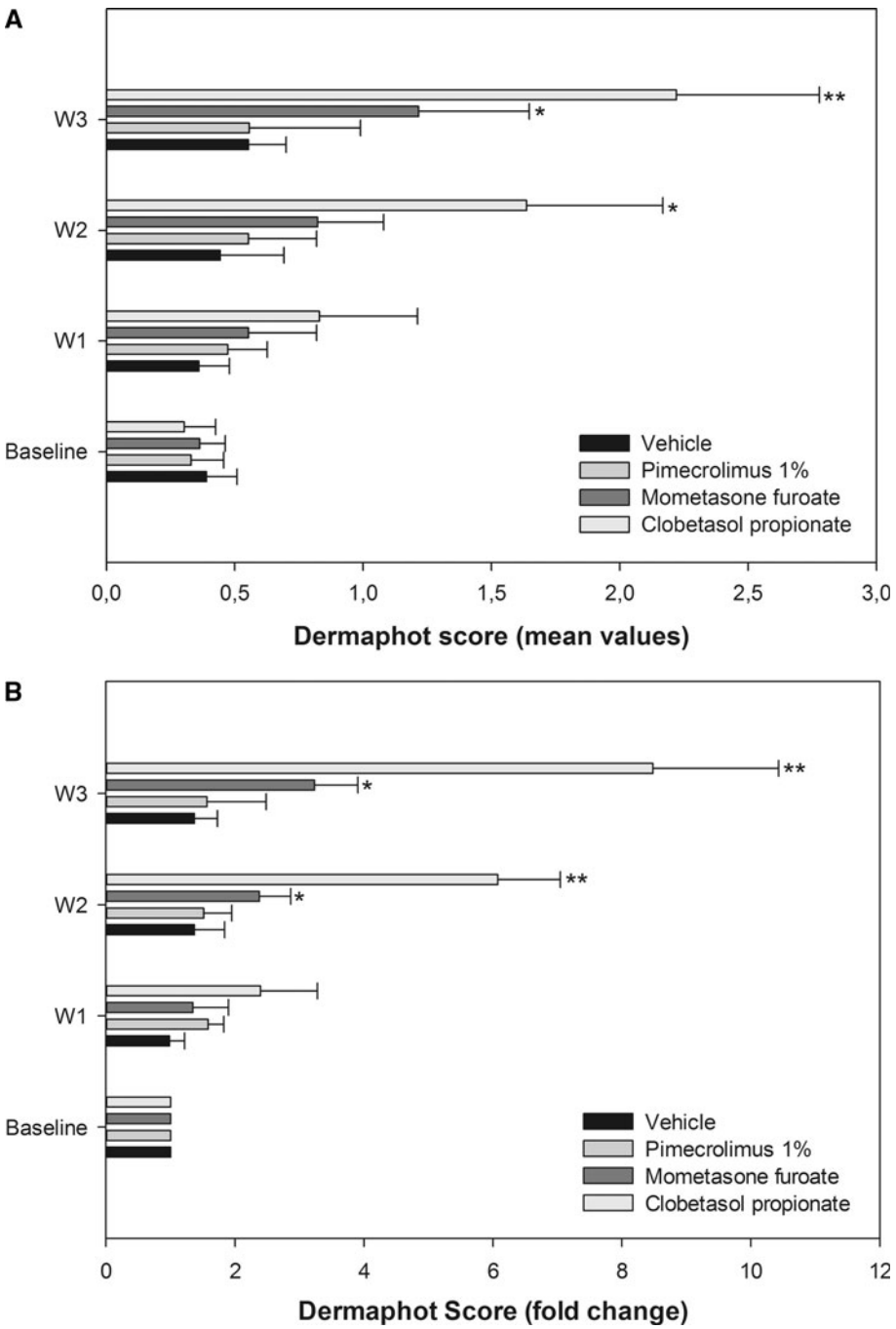

Fig. 2 Dermaphot® assessments of skin areas treated with clobetasol propionate, mometasone furoate, pimecrolimus and vehicle cream. **a** Increase of mean Dermaphot® scores in skin areas treated with steroid ointment. Data are shown as mean ± SEM for $n = 36$ per ointment group. $^{**}p < 0.01$ and $^{*}p < 0.05$ versus vehicle at baseline. **b** Fold increase of Dermaphot® score compared to baseline values for the different ointments. Data are shown as mean ± SEM for $n = 36$ per ointment group. $^{**}p < 0.01$ and $^{*}p < 0.05$ versus vehicle at baseline

verrucae, burning sensation and petechial bleeding) have been documented. Of those, hypopigmentation, erythema, burning sensation and petechial bleeding were classified as possibly related to the study medication. The skin adverse events (hypopigmentation, erythema, burning sensation and petechial bleeding) occurred only in skin areas which were treated which topical GC during the trial. No skin adverse events emerged in the pimecrolimus 1 % and vehicle cream-treated areas. No serious adverse events were observed in the clinical trial. Skin transparency values were mostly recovered to baseline levels in all subjects at the follow-up visit.

Discussion

Topical GCs are still first-line-treatment for chronic inflammatory diseases, e.g. atopic dermatitis. Topical GCs are effective and inexpensive. The potency of topical GCs, however, is often accompanied by local and systemic side

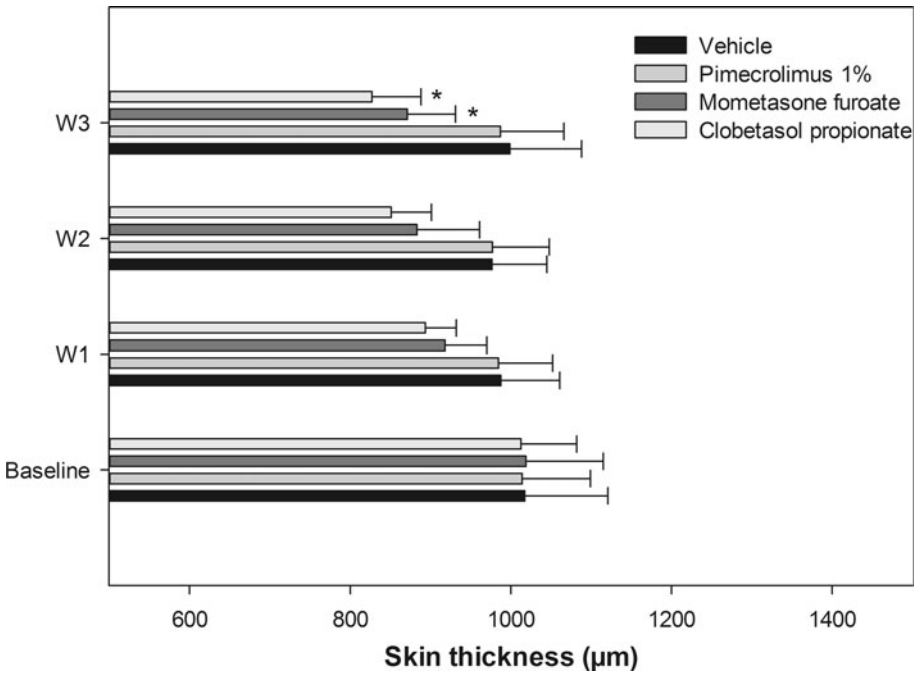

Fig. 3 Ultrasound measurement of the skin thickness in areas treated with steroid and non-steroid creams at baseline and weeks *1*, *2* and *3*. Data are shown as mean ± SEM for $n = 36$ subjects per ointment group. *$p < 0.05$ versus vehicle at baseline (*W1* week 1, *W2* week 2, ff.)

effects, such as skin atrophy, telangiectasia and hypothalamic–pituitary–adrenal axis suppression [8]. Patients applying topical GCs must be well instructed on how to use the cream and to limit the usage for a short-term treatment. The most common side effect, skin atrophy, however, is difficult to measure. Currently, skin atrophy and skin thickness are measured commonly using ultrasound. However, this method requests specific equipment, is time consuming, and is associated with the risk of methodological bias.

Here, we pursued a new approach of dermoscopic assessment to measure and identify early the atrophogenic potential of topical GCs used in the treatment of chronic inflammatory diseases. In addition, this novel attempt simplifies the current methods of atrophy measurements considerably.

To demonstrate that the Dermaphot® score is able to differentiate the extent of skin atrophy a clinical study was performed. Already after 2 weeks a significant increase in skin transparency and telangiectasia was detected with the dermoscopic assessment in areas treated with super-potent topical GC (clobetasol propionate 0.05 %). Transparency in Dermaphot® reflects changes in the epidermal layer including interpapilar areas which means that increased transparency correlates with skin thinning. The induced skin damage was not visible with the naked eye at that early time of onset. Further dermoscopic assessments at week 3 identified also the atrophogenic potential of mid-potent GCs (mometasone furoate; 1 mg/g) and confirmed the week 2 results of the super-potent GCs. Our results showed that the dermoscopic assessment and the Dermaphot® score are able to differentiate the extent of skin atrophy at a very early onset of topical GC use.

Beside topical GCs the subjects applied also pimecrolimus 1 % and vehicle cream. Pimecrolimus 1 % is available as an alternative for the treatment of mild to moderate atopic eczema in subjects 2 years and older in the majority of the countries worldwide including Germany. An important difference in the safety profile of this drug compared with topical GCs is the lack of potential side effects which are often observed upon prolonged use of topical GCs (skin atrophy, steroid-induced rosacea or perioral dermatitis) and hence can be used for the long-term treatment of atopic eczema [9, 16]. The dermoscopic assessments confirmed those findings. Areas treated with pimecrolimus 1 % cream did not show any significant increase in the Dermaphot® score compared to baseline levels and compared to vehicle-treated areas.

In addition, ultrasound measurements were performed on the treated skin areas of all volunteers to measure skin atrophy and to compare ultrasound results with Dermaphot® score values. The ultrasound measurements were calculated only for the epidermal layer and thickness was measured without considering subcutaneous fat tissue which allows comparing between both methods. Ultrasound data showed a rapid decrease of skin thickness in the topical GC-treated areas after 1 week. Moreover, the values decreased at weeks 2 and 3, continuously. In contrast, no significant decrease of skin thickness was detected for the pimecrolimus 1 % cream and the vehicle cream. Looking at the values of ultrasound and Dermaphot® scores for week 2 and week 3 visits, we can conclude that

both methods independently detect the significant reduction in skin thickness of steroid-treated areas.

Safety outcomes of the study were favourable without serious adverse events. All adverse events ($n = 9$) were resolved at the follow-up visit excluding the adverse event "hypopigmentation".

Overall, the current clinical trial fulfilled the primary objective and demonstrated for the first time that the Dermaphot® score can be used as a novel tool to differentiate the extent of skin atrophy after the application of atrophogenic and non-atrophogenic topical formulations. Moreover, the non-atrophogenic potential of pimecrolimus 1 % cream was confirmed by dermoscopic assessments. Pimecrolimus 1 % cream showed no difference compared to vehicle regarding the induction of skin atrophy or telangiectasia. Thus, the present work proposes a new approach to detect the early onset of skin atrophy without the use of ultrasound. The use of the newly developed Dermaphot® score enables dermatologist to monitor effectively the extent of skin atrophy during the treatment course of topical GCs. Furthermore, the closer monitoring allows the physician to adapt the length of topical GC treatment on a per patient basis.

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References

1. Alexander H, Miller DL (1979) Determining skin thickness with pulsed ultrasound. J Invest Dermatol 72:17–19
2. Aschoff R, Schmitt J, Knuschke P, Koch E, Bräutigam M, Meurer M (2011) Evaluation of the atrophogenic potential of hydrocortisone 1 % cream and pimecrolimus 1 % cream in uninvolved forehead skin of patients with atopic dermatitis using optical coherence tomography. Exp Dermatol 20:832–836
3. Drake LA, Dinehart SM, Farmer ER et al (1996) Guidelines for the use of topical glucocorticosteroids. J Am Acad Dermatol 35:615–619
4. Frosch PJ, Behrenbeck EM, Frosch K, Macher E (1981) The Duhring chamber assay for corticosteroid atrophy. Br J Dermatol 104:57–65
5. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ (2006) Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 54:1–15
6. Kao JS, Fluhr JW, Man MQ et al (2003) Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis account for functional abnormalities. J Invest Dermatol 120:456–464
7. Kligman AM, Frosch PJ (1979) Steroid addiction. Int J Dermatol 18:23–31
8. Pels R, Sterry W, Lademann J (2008) Clobetasol propionate–where, when, why? Drugs Today 44:547–557
9. Queille-Roussel C, Paul C, Duteil L et al (2001) The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. Br J Dermatol 144:507–513
10. Schoepe S, Schäcke S, May E, Asadullah K (2006) Glucocorticoid therapy-induced skin atrophy. Exp. Dermatol 15:406–420
11. Schoepe S, Schäcke H, Asadullah K (2011) Test systems for the determination of glucocorticoid receptor ligand induced skin athrophy. Dermato-Endocrinol 3:175–179
12. Sterry W, Asadullah K (2002) Topical glucocorticoid therapy in dermatology. Ernst Schering Res Found Workshop 40:39–54
13. Tan CY, Statham B, Marks R, Payne PA (1982) Skin thickness measurement by pulsed ultrasound: its reproducibility, validation and variability. Br J Dermatol 106:657–667
14. Vázquez-López F, Marghoob AA (2004) Dermoscopic assessment of long-term topical therapies with potent steroids in chronic psoriasis. J Am Acad Dermatol 51:811–813
15. Vázquez-Lopez F, Pérez-Oliva N (2005) Usefulness of the dermoscope for evaluating the depth of venular malformations. Pediatr Dermatol 22:283
16. Werfel T (2009) Topical use of pimecrolimus in atopic dermatitis: update on the safety and efficacy. J Dtsch Dermatol Ges. 7:739–742