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CLINICAL REPORT

Anti-pruritic Effect of Sertaconazole 2% Cream in Atopic Dermatitis Subjects: A Prospective, Randomized, Double-blind, Vehicle-controlled, Multi-centre Clinical Trial of Efficacy, Safety and Local Tolerability

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This study was a prospective, parallel-group, randomized, double-blind, vehicle-controlled, multi-centre clinical trial to compare the efficacy of topical sertaconazole 2% cream with vehicle in reducing chronic pruritus in subjects with atopic dermatitis, and to assess its safety and local tolerability. A total of 70 subjects applied either of the 2 treatments twice daily for a period of 4 weeks on affected, itchy skin areas. Treatment efficacy was evaluated primarily considering the item itch intensity on a 5-point verbal rating scale. Insomnia, state of atopic dermatitis (Scoring Atopic Dermatitis; SCORAD), quality of life and therapy benefit were also assessed. No significant difference between active treatment and vehicle was found at any of the time-points for any of the investigated parameters. Under the experimental conditions of the study, sertaconazole 2% cream did not exert anti-pruritic effects that were better than vehicle in subjects with atopic dermatitis who had chronic pruritus. Trial registration ClinicalTrials.gov #NCT01792713. *Key words: sertaconazole; pruritus; itch; atopic dermatitis*.

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Atopic dermatitis (AD), one of the most pruritic skin diseases (1, 2), is a common disorder affecting 15–30% of children and 2–10% of adults in industrialized countries (3). Pruritus, the unpleasant sensation that leads to a desire to scratch (4), is the most important clinical symptom of AD (5, 6) with a prevalence of up to 100% in this disease (7). The exact pathophysiology of itch in AD is not yet fully understood (8). Studies have demonstrated that mechanisms such as increased density of cutaneous nerve fibres participate in the induction and maintenance of this troublesome and disabling symptom, in addition to various receptors (cold receptor TRPA1, histamine 4 receptor, proteinase activated receptor 2/Mas-related G protein receptor) and central and peripheral mediators, e.g. histamine, nerve growth factor (NGF), substance P (SP), proteases, and cytokines/chemokines (thymic stromal lymphopoietin (TSLP), interleukin (IL) -2, IL-4, IL-13, prostaglandin E2 and IL-31) (1, 7-9). In severe cases of AD, subjects scratch the involved skin areas until they bleed (1). This worsens the skin condition, resulting in a vicious itch-scratch cycle, which severely affects the quality of life of subjects and their families (6). Itch management is, therefore, one of the most important issues in the treatment of AD (10). There is no generally established therapy for itch in AD. Hence, atopic pruritus is usually treated with a tailored approach (11), either with moisturizers or with topical and systemic immunosuppressants (12). Although such therapies generally have a good safety profile, better itch-specific treatment options are needed.

Systemic and/or topical antimycotics of the imidazole type have been reported to be effective in AD (13–15). Their fungistatic or fungicidal effects can explain this as fungi, such as *Malassezia furfur*, are involved in AD. However, direct immunomodulatory effects have also been reported to be responsible for their efficacy in AD (15). Sertaconazole nitrate is a well-established, well-tolerated, commercially available (Dermofix®, Ertaczo™, Ginedermofix®, Monazol, Mykosert® or Zalain®) imidazole antifungal agent, which also exerts anti-bacterial action (16). Sertaconazole nitrate has been shown to reduce the release of cytokines from activated lymphocytes and to mitigate inflammation in animal models of irritant contact dermatitis and neurogenic inflammation (17). Furthermore, sertaconazole reportedly inhibits contact hypersensitivity and scratching responses in a murine model of substance P-induced pruritus, indicating that topical administration may result in an efficacious anti-inflammatory activity in a spectrum of cutaneous inflammation models and itch (17). Kaur et al. (18) have shown that sertaconazole mediates its anti-itch effects by increasing prostaglandin D2 levels in mast cells and macrophages through induction of the p38 mitogen-activated protein kinase pathway. Prostaglandin D2 is known to have anti-pruritic activity by suppressing histamine release (19). Finally, human studies in fungal infections reported

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anti-pruritic effects from antimycotic treatment with sertaconazole (20–22). Therefore, sertaconazole with its positive safety profile (16) and its anti-inflammatory and anti-pruritic properties could be a possible solution to address pruritus in AD. However, clinical studies evaluating its anti-pruritic action in AD are sparse and, as yet, there are no published reports of controlled studies. Thus, the aim of this study was to close this gap, by comparing the efficacy of topical sertaconazole 2% cream with vehicle in reducing chronic pruritus in subjects with AD, as well as to assess its safety and local tolerability.

METHODS

Study design

This was a prospective, randomized (1:1), double-blind, vehicle-controlled, parallel-group, phase-II clinical trial conducted at 2 sites in Germany (Center for Chronic Pruritus, Department of Dermatology, University Hospital Münster; Allergie-Centrum-Charité, Department of Dermatology and Allergy, Charité –Universitätsmedizin Berlin, Germany). All subjects gave written informed consent. The ethics committee at the central coordinating centre (Münster) and at the participating site (Berlin) both approved the trial. The trial is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT01792713 and at the European Union Clinical Trial Register.

Study population and treatment

Over a period of 11 months, 70 randomly (1:1) selected subjects (30 males, 40 females, 18–75 years, mean age 34.1 (± 14.7) years) with pruritus (> 6 weeks, visual analogue scale (VAS) ≥ 7, (VAS 0–10) during the last 2 days before visit 1; verbal rating scale (VRS) ≥ 3) due to AD (Scoring Atopic Dermatitis; SCORAD ≤ 40) were included in the study. Subjects showing unstable or uncontrolled significant medical conditions, infections, addiction to alcohol or/and drugs, dermatological abnormalities, allergy to any of the treatment's ingredients, participation in another clinical study, pregnancy or lactation or using therapies up to 2 or 4 weeks before onset of the study, which could influence its outcome (antihistamines, corticosteroids, immunomodulators, naltrexone, antidepressants, immunosuppressants, topical calcineurin inhibitors, topical antibiotics, antiseptics) were excluded from participation in this trial.

Thirty-two subjects were treated with sertaconazole 2% cream and 38 with the cream's vehicle (cream manufactured by the sponsor to match exactly appearance, odour and consistency of the active cream) (Fig. 1). To ensure full blinding (assessors, care-givers, subjects), active and vehicle creams were both in neutral tubes and were randomized, labelled and delivered directly to the sites by a clinical services provider. In the centres, investigators chose a kit at random and after recording the number in the case report form it was given to the subject. Treatment was carried out twice daily, as indicated for the commercial cream Mykosert® (Dr. R. Pfleger Chemische Fabrik GmbH, Bamberg, Germany), during 4 weeks on affected itchy skin areas determined by the investigator, followed by a 2-week treatment-free wash-out period. Subjects were allowed to use moisturizing cream (Excipial® Hydrocreme (Galderma-Spirig, Egerkingen, Switzerland)) with no additional therapy during the whole study. Adherence to treatment was assessed by collecting and weighing the treatment tubes at each subject visit.

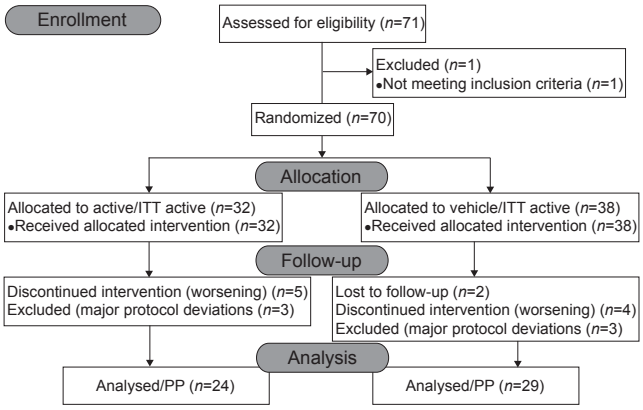

Fig. 1. Progress of all subjects through the trial. PP: per-protocol population.

Study outcomes

The primary efficacy success was defined as ≥ 2 grades reduction in intensity of pruritus between baseline and week 4, as evaluated on a 5-point VRS, which was part of the patient's global assessment (PGA) questionnaire. The subject answered this at each visit under the supervision of the investigator. Further efficacy variables were: intensity of pruritus and insomnia both on a VAS, state of atopic dermatitis (SCORAD, Eczema Area and Severity Index (EASI)) and of quality of life (Dermatological Life Quality Index (DLQI)). The Patients Benefit Index (PBI) questionnaire was used to evaluate the subjects' appreciation of the treatment benefits vs. baseline, and featured 27 items. Each of the 27 items had to be answered as not at all, slightly, moderately, quite a lot or as very much. Skin barrier function (transepidermal water loss (TEWL)), mycological evaluation of skin surface, adverse events, vital signs and blood laboratory parameters were also assessed during the course of the study. All scales used are generally recognized as reliable, accurate and relevant for subjects with atopic dermatitis (6, 23, 24).

Statistical methods

To achieve a ≥ 2 point decrease in pruritus intensity during treatment in 60% of the active treated and in 30% of the vehicle-treated subjects, with a statistical power of ≥ 80% and a significance level at $p \leq 0.05\%$, the sample size was estimated at 40 subjects per group (due to recruiting difficulties a final total of 70 subjects was included in the study). The null hypothesis was defined as the success/failure ratio in both groups being the same. Statistical testing was conducted with a 2-sided χ^2 test with Yates corrections. Statistical analysis of the secondary parameters (mean intensity of itch (VAS) and mean SCORAD) was conducted via analysis of covariance (ANCOVA) with baseline as a covariate and treatment as a factor. For EASI, statistical analysis was waived before outcome results were available, because at evaluation it appeared that the 2 centres performed the EASI assessments in a different manner. Efficacy data were analysed at each visit based on the per-protocol (PP) population, excluding major deviations that were identified during a blind review of the data. In addition, an intention-to-treat (ITT) analysis was performed on all randomized subjects after inputting missing data using the last observation carried forward (ITT-LOCF). The Safety Population was defined as comprising the ITT-LOCF population. All safety data were summarized based on the Safety Population.

RESULTS

Efficacy

Between February and December 2013 a total of 71 subjects was screened for eligibility (Fig. 1). Seventy subjects met the eligibility criteria (ITT-LOCF) and were randomized either to active treatment ($n=32$) or to vehicle ($n=38$) (Fig. 1). Among these subjects, 17 presented major protocol deviations (omission of pruritus assessments, interfering concomitant treatments, visits outside the window foreseen). Thus, the remaining 53 subjects composed the PP population ($n=24$ active treated, $n=29$ vehicle treated). Demographics and baseline clinical characteristics were similar in both groups (Table I). No differences regarding compliance were apparent between treatments or between centres.

In the ITT-LOCF population (Table II), a total of 5 subjects (16%) in the active group and 8 subjects (21%) in the vehicle group achieved the primary objective of 2 grades reduction in itch intensity (VRS) between baseline (visit 1) and week 4 (visit 3) ($p=0.78$). Between baseline and week 2 (visit 2), 5 subjects (16%) in the active and 4 (11%) in the vehicle group achieved the targeted reduction ($p=0.78$), and between baseline and week 6 (visit 4), 7 (26%) active treated subjects and 5 (16%) receiving vehicle achieved 2 grades reduction ($p=0.51$). Looking at only one grade reduction (Table II) in itch intensity (VRS) between visits 1 and 3, again no statistically significant differences between active treatment ($n=7$, 39%) and vehicle ($n=11$, 52%) were found ($p=0.62$), and the same was observed between visits 1 and 2 ($p=0.56$) and between visits 1 and 4 ($p=0.25$). The overall results were similar in the PP population (Table SI[1]) and when comparing both centres.

With regard to the secondary criteria, pruritus intensity, as evaluated by VAS, decreased during the study slightly more in the active group (ITT-LOCF: 3.3 cm; PP 3.5 cm) than in the vehicle group (ITT-LOCF 2.2 cm; PP 2.1 cm) (Tables II and SI[1]). However, these differences were not statistically significant (ITT-LOCF $p=0.101$; PP $p=0.09$) (Tables II and SI[1]). Similarly, during the course of the study, insomnia rates (VAS) (only the PP population was considered) also decreased slightly, but not significantly, more in the active (from 7.8 ± 0.7 cm to 3.2 ± 2.1 cm) than in the vehicle group (from 5.7 ± 2.6 cm to 3.7 ± 2.7 cm) (Table SI[1]).

SCORAD remained stable over the study duration without statistically significant differences between active and vehicle, either at visit 3 (ITT-LOCF: $p=0.21$, PP: $p=0.58$) or at visit 4 (ITT-LOCF: $p=0.25$, PP: $p=0.18$) (Tables II and SI[1]).

The continuous data evaluation of the quality of life (DLQI) values, which were analysed only in the PP population, decreased in the active group by 3.1 (from 9.3 ± 4.2 to 6.2 ± 4.9) and in the vehicle group by approximately 4.2 (from 11.4 ± 6.3 to 7.2 ± 5.6) scores (Table SI[1]). In the same way, the categorical analysis of the DLQI (sum of the percentages of ''not at all'' and ''little'' effect on subject's life) increased from 13% (visit 1) to 44% (visit 3) in the active group and from 21% (visit 1) to 48% (visit 3) in the vehicle group.

The possible benefit of the therapy, as evaluated by the subject (PBI: Patient Benefit Index), showed that at the end of the treatment (visit 3), almost all questions were answered with ''Treatment helped not at all'' by both groups. The cosmetic items evaluated (desquamation, feeling of tenseness and burning sensation) remained stable during the study, with the exception of skin roughness, which showed a tendency to decrease (from 5.2 ± 2.4 at visit 1 to 2.7 ± 0.9 at visit 4) in the active group (Table SI[1]).

During the course of the study, TEWL of lesional and non-lesional skin remained stable in both groups (active and vehicle) including the treatment-free washout phase (Table SI[1]).

Overall, the results also remained the same when analysing all primary and secondary efficacy parameters for the 2 centres individually. No significant difference in treating pruritus in subjects with mild to moderate AD could be revealed between the sertaconazole 2% cream and the vehicle cream.

Safety

No safety issues were identified for either treatment during the study duration. The skin barrier function was not significantly influenced by the treatments. A total of 35 subjects (active 16, vehicle 19) reported 52 (active 25, vehicle 27) adverse events during the treatment phase. Thirty-three of these adverse events were dermatological (mostly AD worsening), of which 28 could be related to the treatments (active

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Table I. *Subject demographics and atopic dermatitis (AD) characteristics*

	Active		Vehicle	
Characteristic	ITT	PP	ITT	PP
Total, *n*	32	24	38	29
Female, *n* (%)	16 (50)	13 (54)	24 (63)	17 (59)
Age, mean (SD)	37 (16.3)	36.7 (16.1)	31.7 (12.8)	31.7 (13.1)
AD family history, *n* (%)	16 (50)	10 (42)	20 (53)	16 (55)
Asthma as child, *n* (%)	8 (25)	6 (25)	16 (42)	11 (38)
Chronic pruritus, *n* (%)	32 (100)	24 (100)	38 (100)	29 (100)
Allergic rhinitis, *n* (%)	21 (66)	17 (71)	24 (63)	20 (69)
Xerosis/dry skin, *n* (%)	32 (100)	24 (100)	37 (97)	28 (97)
Mycological evaluation, positive, *n*	0	0	1	0
Age at first appearance, mean (SD)[a]	9 (19.1)	6.9 (17.8)	6.8 (15.5)	5.7 (14.8)
AD relapses during the last year, mean (SD)	7.6 (5.7)	6.3 (4.9)	9.1 (8.2)	10 (8.9)

[a]Age of the subject at first appearance of atopic dermatitis symptoms.
SD: standard deviation; ITT: intention-to-treat population; PP: per-protocol population.

Table II. *Efficacy results and evolution of the main criterion (itch intensity from verbal rating scale) from day 0 to day 42 in the intention-to-treat-last observation carried forward (ITT-LOCF) population*

		ITT-LOCF population					
Itch/VRS	Therapy	Visit 1 Day 0	Visit 2 Day 14		Visit 3 Day 28		Visit 4 Day 42	
Grades, *n* (%)								
1	Active	0 (0)	0 (0)		1 (3)		0 (0)	
	Vehicle	0 (0)	0 (0)		1 (3)		0 (0)	
2	Active	0 (0)	4 (13)		6 (19)		7 (26)	
	Vehicle	0 (0)	7 (18)		10 (26)		6 (19)	
3	Active	3 (9)	8 (25)		9 (28)		12 (44)	
	Vehicle	10 (26)	8 (21)		6 (16)		9 (28)	
4	Active	24 (75)	11 (34)		9 (28)		5 (19)	
	Vehicle	22 (58)	15 (39)		16 (42)		10 (31)	
5	Active	5 (16)	9 (28)		7 (22)		3 (11)	
	Vehicle	6 (16)	8 (21)		5 (13)		6 (19)	
Primary criterion itch intensity[a]								
VRS ≥2, *n* (%) (*p*)	Active		5 (16)	$p=0.7822$	5 (16)	$p=0.7847$	7 (26)	$p=0.517$
	Vehicle		4 (11)		8 (21)		5 (16)	
VRS ≥1, *n* (%) (*p*)	Active		12 (38)	$p=0.7123$	15 (47)	$p=0.9836$	19 (70)	$p=0.1199$
	Vehicle		17 (45)		19 (50)		15 (47)	
VRS <1, *n* (%) (*p*)	Active		20 (62)	$p=0.7123$	17 (53)	$p=0.9836$	8 (30)	$p=0.1199$
	Vehicle		21 (55)		19 (50)		17 (53)	
Secondary criteria								
Pruritus VAS, cm, mean (SD)	Active	7.7 (0.7)	6.5 (2.6)		5.6 (2.7)		4.4 (2.4)	
	Vehicle	7.8 (0.7)	6.5 (2.5)		5.9 (2.9)		5.6 (2.9)	
SCORAD, mean (SD)	Active	35 (5.0)			38.3 (15.0)	$p=0.2128$	29.2 (12.6)	$p=0.2504$
	Vehicle	35.2 (5.4)			34.3 (12.5)		32.9 (12.7)	

[a]Verbal rating scale (VRS) ≥2: primary criterion i.e. number of subjects presenting at least 2 grades reduction from baseline to week 4 on the item itch intensity of the 5-point VRS; VRS ≥1 or <1: revised primary criteria to determine potential significant differences.
VAS: visual analogue scale; SD: standard deviation; SCORAD: Scoring Atopic Dermatitis.

15, vehicle 13). Finally, no differences between the 2 groups or a trend concerning concomitant medication used to treat AD or adverse events during the study were apparent.

DISCUSSION

The present study was designed with the main objective of demonstrating the anti-pruritic effect of sertaconazole 2% cream vs. vehicle in subjects with AD who had severe, chronic pruritus. The study failed to confirm this hypothesis. Under the experimental conditions of the study, the investigated sertaconazole 2% cream showed a small anti-pruritic effect, which was not significantly different from that of the vehicle treatment. Of the criteria assessed, only the items itch intensity and insomnia (both VAS) and skin roughness (VRS) showed a tendency for a possibly stronger effect of sertaconazole. However, these effects achieved no significance vs. vehicle (Table SI[1]). In the case of SCORAD, the clinically meaningful decrease of at least 4 points (25) was reached only with the vehicle treatment without clinical significance vs. the active therapy. The fact that TEWL remained stable during the whole study in both lesional and non-lesional skin indicated that neither treatment influenced the skin barrier function (26).

Similar observations were also made in 2 other clinical studies in which a topical azole was either added or compared with hydrocortisone 1%. Wong et al. (27) found that the addition of an antifungal ointment (miconazole cream) to 1% hydrocortisone cream did not add any benefit to the topical corticosteroid treatment in flexural AD. More recently, Saki et al. (28) compared the effect of topical sertaconazole 2% cream and hydrocortisone 1% ointment in the treatment of AD in a double-blind bilateral study with 45 subjects aged 6 months to 32 years. The duration of treatment was 4 weeks. A modified SCORAD score was applied to assess the severity of the disease before and after treatment. This study also found no significant difference between the 2 drugs in decreasing single symptoms, such as pruritus or erythema, i.e. both drugs improved the symptoms to the same extent. However, sertaconazole was significantly better in decreasing the total AD score ($p=0.023$). Besides the fact that this study had a different design from ours (bilateral), subjects had to discontinue any other topical or systemic preparation, including basic emollients, which could be a possible explanation for the more positive outcome.

One could argue that, in our study, due to the stable, non-inflammatory state of AD at inclusion, it was difficult to significantly influence the scores. In addition, subjects were allowed to use a basic emollient cream (Excipial® Hydrocreme) ad libitum during the whole

duration of the study, which might also have influenced the outcome. Application of moisturizers has been reported to be able to decrease symptoms and signs of AD, including pruritus (12). Finally, in human studies, an anti-pruritic effect has so far been shown only for sertaconazole in dermatoses associated with fungal infections, e.g. seborrhoeic dermatitis, head and neck dermatitis with involvement of *Malassezia*, tinea pedis or vaginal candidiasis. This suggests that the outcome of the study could have been different if only fungus-infected AD cases had been included in the study.

In conclusion, no significant anti-pruritic effect can be expected from sertaconazole 2% cream in subjects with mild to moderate stable AD. However, it is not known if higher concentrations of sertaconazole or different formulations have a different effect. The anti-pruritic effect reported in the treatment of fungal infections is probably linked to its antifungal action.

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