International Journal of Clinical Pharmacology and Therapeutics, Vol. 45 – No. 11/2007 (583-591)

ISSN 0946-1965

A randomized, double-blind, vehicle-controlled, half-side comparison with a herbal ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica for the treatment of mild-to-moderate atopic dermatitis

W. Klövekorn[1], A. Tepe[1] and U. Danesch[2]

[1]Dermatology Practice, Gilching, [2]Weber and Weber GmbH and Co. KG, Research and Development, Inning, Germany

Key words
atopic dermatitis – adults – herbal ointment – Ekzevowen®

Abstract. Objective: Only a few clinical trials have been published on the topical treatment of atopic dermatitis with herbal ointments. An ointment containing extracts from Mahonia aquifolium, Viola tricolor and Centella asiatica has previously been studied in open uncontrolled trials with children. However, no data exist on adult patients in a randomized controlled trial. Methods: A total of 88 patients with mild-to-moderate atopic dermatitis were enrolled in a double-blind, vehicle-controlled, randomized, half-side comparison. Patients between 18 and 65 years of age were treated for 4 weeks with an ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica. The primary endpoint was a summary score for erythema, edema/papulation, oozing/crust, excoriation and lichenification according to a 4-point scale. Secondary efficacy variables were assessment of pruritus severity (10 cm VAS) and a global assessment of effectiveness as well as tolerability. Results: The study ointment reduced the primary and secondary endpoints slightly more than the base cream which was used as vehicle; the differences were not statistically significant. Since the climatic conditions during the study duration varied from very mild and sunny to very cold and dry, a post-hoc subanalysis was performed with a subset of 64 patients whose treatment was at a mean outside temperature of 10 °C or less. Under these conditions the primary endpoint showed high statistical significance. Conclusion: In this trial, an ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica could not be proven to be superior to a base cream for patients with mild-to-moderate atopic dermatitis. However, a subanalysis indicated that the cream might be effective under conditions of cold and dry weather.

Received
February 9, 2007;
accepted
July 19, 2007

Correspondence to
Dr. W. Klövekorn
Hautarztpraxis,
Römerstraße 4,
82205 Gilching,
Germany
dr.kloevekorn@
t-online.de

Introduction

Atopic dermatitis is a chronic inflammatory disease of the skin which can significantly affect a patient's health and well-being [Hanifin and Rajka 1980, Rajka and Langeland 1989]. Approximately 10 – 20% of children and 1 – 3% of adults are affected [Williams et al. 1999]. The most common symptoms of atopic dermatitis are pruritus and erythema. Atopic dermatitis often coexists with other atopic diseases, such as asthma, rhinitis and allergic conjunctivitis. The precise cause of atopic dermatitis is not known but many immunological and environmental factors contribute to this disease [Novak et al. 2003]. Atopic persons have elevated serum IgE levels and increased peripheral eosinophils. In addition, certain T cell-produced cytokines are either elevated or decreased [Leung et al. 2004]. Another common feature is a defect in the skin barrier function resulting in an increased loss of moisture from the epidermal layer reducing the skin's protective abilities [Schafer and Kragballe 1991]. Corticosteroids and more recently the immunomodulators and calcineurin inhibitors tacrolimus and pimecrolimus have generally been used for the topical treatment of atopic dermatitis. Both substances are not without certain hazards where skin atrophy [Kolbe et al. 2001] is a known side effect of topical corticosteroids as well as possible growth retardation in children. The immunomodulators are linked to cancer in animal studies but long-term safety data in humans are missing [Bieber et al. 2005]. Therefore, many patients and parents of afflicted children prefer natural

(herbal) alternatives. Phytotherapeutic preparations have been used in conventional dermatology for a long time. Many different herbal preparations have been tested in experimental systems and on patients with various dermatologic conditions [Bedi and Shenefelt 2002, Brown and Dattner 1998, Levin and Maibach 2002]. Although it is possible to evaluate herbal medicines in much the same way as conventional drugs, only a few herbal extracts have been studied as a topical treatment for atopic dermatitis in randomized, vehicle-controlled clinical trials [Ernst 2004]. Published results are available for St. John's wort cream, a chamomile cream, a hamamelis cream and a licorice gel [Korting et al. 1995, Patzelt-Wenczler and Ponce-Poschl 2000, Saeedi et al. 2003, Schempp et al. 2003]. All trials were performed with small numbers of patients.

The herbal ointment used in this study contains alcohol-based plant extracts of Mahonia aquifolium (Berberis aquifolium), Viola tricolor and Centella asiatica (Hydrocotyle) and their ingredients as pharmacological active substances prepared according to the "Homöopathisches Arzneibuch" and a base formulation according to the "Deutsche Arzneimittel-Codex" (DAC). Positive monographs of the "Kommission D" are available for all three herbals. The study medication is available in Germany (Ekzevowen derma®), UK (Linderma®) and in the USA (Dermavex®). So far, the ointment has been studied in two open trials with 52 and 27 children with mild-to-moderate atopic dermatitis, respectively [Abeck et al. 2005]. The ointment was very well tolerated and all symptoms of eczema were markedly reduced.

The current study was conducted to determine efficacy and safety in a controlled and randomized clinical trial with adult patients suffering from mild-to-moderate atopic dermatitis.

Methods

The trial was conducted as a randomized, double-blind and controlled half-side comparison study. The trial took place in a dermatology practice in Southern Germany from March 2005 until April 2006.

Subjects

Patients provided written informed consent prior to enrolment. This study was conducted in accordance with the ethical standards of Good Clinical Practice, the scientific guidelines of the EMEA and the regulations of the Declaration of Helsinski and was approved by the Institutional Review Board of the State of Bavaria.

Patients were Caucasian males or females between 18 and 65 years of age with mild-to-moderate atopic dermatitis. Atopic dermatitis was diagnosed based on Hanifin and Rajka [1980] and graded according to Rajka and Langeland [1989] criteria. In order to be included into the study the grading of atopic dermatitis had to be at least 3 and not more than 7 points.

For the evaluation of efficacy the inward bend of each elbow was used as target area. At inclusion, both elbows were not allowed to differ by more than 2 points regarding the severity of the summary score for the primary endpoint. If the elbows did not qualify as target area, the inward bend of each knee was assessed instead using the same inclusion criteria.

Patients were excluded for the following conditions: application of oral glucocorticoids during 4 weeks prior to the study entry, systemic treatment with antihistamines, antipruritic or immunosuppressive agents for at least 14 days prior to the study, any drug treatment (including topical glucocorticoids, UV, urea etc.) of the test area (elbow or knee) for at least 14 days prior to the study, severe cardiovascular disease, liver or kidney insufficiency, respiratory insufficiency, neoplasm, any acute or chronic disease causing a severe impairment of the patient's general condition, abuse of alcohol, medication, drugs or nicotine, hypersensitivity to the ointment base and/or hypersensitivity to one of the active ingredients (Mahonia aquifolium, Viola tricolor or Centella asiatica), current or previous participation in a clinical trial within 1 month prior to study entry and pregnancy or nursing and/or women in childbearing age without effective contraception.

During the study, the use of the following therapies, either systemic or topical on the target area, were not allowed: glucocorticoids, antihistamines, antipruritic agents, topical nonsteroidal antiinflammatory drugs, antimi-

crobials, urea, coal tar, UV treatment, phototherapy, immunosuppressive agents.

Patients were free to withdraw from the study at any time at their own request or at the request of their legally authorized representative without giving any reason for withdrawal. Due to this measure no escape medication was offered which would have interfered with the study outcome.

Study design and treatment

Treatment with the study medication and the vehicle was randomly allocated in a double-blind manner to the left or right side of the body, respectively. The computer-generated randomization code was prepared by a statistician not involved in data management and statistical analysis. To maintain blindness of the study, verum and vehicle were similar in appearance and were dispensed in identical tubes labelled right and left body side. Each patient received a consecutive patient number based on the order of recruitment into the study. The patient number randomized the patients to the treatment of the left and right body side including the target area in a double-blind fashion. The patient number appeared on the study medication and the case record forms. The herbal ointment used in the study contains alcohol-based plant extracts of Mahonia aquifolium (Berberis aquifolium), Viola tricolor and Centella asiatica (Hydrocotyle) (5 g each per 100 g ointment) prepared according to the "Homöopathisches Arzneibuch" and based on a DAC formulation. The DAC base formulation (vehicle) was used as comparator. A thin layer of herbal ointment or vehicle alone was applied twice daily to all affected areas for a total of 4 weeks. Every patient treated each side of the body separately, e.g. one side of the body with verum, the other side of the body with vehicle in a blinded and randomized fashion. Patients were extensively and carefully instructed by the physicians how to apply the study medications and to wash or wipe hands when changing body sites.

Drug accountability and compliance were checked by medication return and documentation of application frequencies. Patients will be regarded noncompliant if the application was less than 75%.

Efficacy evaluations

The primary endpoint was based on the change of the summary score for erythema, edema/papulation, oozing/crust, excoriation and lichenification of the target area between the first day (baseline) and last day (completion) of treatment and compared between verum and vehicle. Each symptom was assessed by the investigator using a standard severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Secondary efficacy variables were assessment of pruritus severity of the target area by the patient using a 10 cm VAS (0 cm = no itch, 10 cm = worst itch imaginable), individual scores for erythema, edema/papulation, oozing/crust, excoriation and lichenification and a global assessment of effectiveness by the patient and the investigator, respectively, according to a 6-point verbal scale (1 = symptoms completely resolved, 2 = symptoms markedly improved, 3 = symptoms moderately improved, 4 = symptoms slightly improved, 5 = symptoms unchanged, 6 = symptoms worse).

For safety, adverse events were documented at each of the two visits after 14 days of treatment and at the end of treatment. Also, an overall assessment of the tolerability of the medication compared to Day 1 was conducted by the patient and the investigator, respectively, according to a 4-point verbal scale (0 = excellent, 1 = good, 2 = moderate, 3 = poor) after 14 days of treatment and at the end of treatment.

Statistical analysis

For the confirmatory efficacy analysis of the primary endpoint, a total of 70 evaluable patients were calculated to be required. This would detect a 20% difference between verum and vehicle with a 2-tailed significance level of 5% and a power of 80%. Taking an overrecruitment rate of 20% into account, 88 patients were enrolled into this study.

The database was generated by using double data entry with electronic verification upon second entry, followed by subsequent checks for completeness and plausibility according to a validation plan. Data Query Forms were sent to the investigator for further clarification if necessary.

Table 1a. Demographics and baseline characteristics for the overall ITT-population (n = 88) and the post-hoc "temperature" subset (n = 64).

Demographic characteristics	n = 87	n = 64
Age/yr	38.6 ± 15.6	39.1 ± 15.5
Sex/no. (%)		
Female Male	57 (65.5) 30 (34.5)	39 (60.9) 25 (39.1)
Height/cm	169.7 ± 8.6	170.3 ± 8.7
Weight/kg	68.7 ± 13.6	69.9 ± 13.3
Body mass index/kg/m^2	23.7 ± 3.6	24.0 ± 3.3
Baseline characteristics: Dermatitis		
Diagnosis Hanifin and Rajka		
Major symptoms	3.9 ± 0.3	4.0 ± 0.2
Minor symptoms	12.9 ± 2.8	13.5 ± 2.5
Grading Rajka and Langeland		
Score summation	5.2 ± 1.1	5.2 ± 1.0
Mild (3 – 4)	23 (26.4)	17 (26.6)
Moderate (4.5 – 7.5)	64 (73.6)	47 (73.4)
Severe (8 – 9)	0 (0.0)	0 (0.0)
Extent/no. (%)		
Less than 9% body area	54 (62.1)	37 (57.8)
Between 9% and 36%	30 (34.5)	24 (37.5)
More than 36%	3 (3.4)	3 (4.7)
Course/no. (%)		
More than 3 months remission	40 (46.0)	28 (43.8)
Less than 3 months remission	22 (25.3)	19 (29.7)
Continuous	25 (28.7)	17 (26.6)
Intensity/no. (%)		
Mild itch, exception. dist. sleep	24 (27.6)	19 (29.7)
Between mild and severe	46 (52.9)	34 (53.1)
Severe itch, usual dist. sleep	17 (19.5)	11 (17.2)
Target site		
Elbow/no. (%)	69 (79.3)	54 (84.4)
Knee/no. (%)	18 (20.7)	10 (15.6)
Duration current symptoms/month	1.3 ± 3.3	1.5 ± 3.8
Time to first diagnosis/yr	11.6 ± 10.5	11.6 ± 11.0
Involved body area/%	8.8 ± 8.1	9.6 ± 8.6

Values are means ± standard deviation.

All analyses were performed with the intention-to-treat data set using a 1-sample Wilcoxon signed rank test for the pre-post-differences comparing verum and vehicle. The significance level is $\alpha = 5\%$ (2-sided). The last-value-carried-forward method was applied throughout all performed testing.

Results

Baseline characteristics

A total of 88 patients with mild-to-moderate atopic dermatitis were enrolled and 87 patients were included for the analysis of the various endpoints. One patient was excluded from the analysis since he did not provide a valid post-baseline value. 17 patients terminated the study prematurely due to lack of efficacy, 4 regarding the vehicle-treated side, 1 regarding the verum-treated side and 12 regarding both treatment sites. The compliance was 99% based on the premise that study medication had to be applied during 75% of the study days.

For demographics and baseline characteristics see Tables 1a and 1b. Because the study was designed as half-side comparison, all patient-related prognostic factors (e.g. demographics and grading/diagnosis of dermatitis) are identical. Since according to the inclusion criteria at baseline the verum and vehicle target area may not differ by more than 2 points in severity of the summary score, the verum and vehicle target area can be assessed as having equal baseline and no tests for homogeneity were required. In fact, Tables 1a and 1b show that the baseline for the summary score and the individual scores in the two target areas were identical.

Efficacy

The summary score improved for both target areas after 2 and 4 weeks of treatment. As Table 2 shows, the improvement for the verum site was greater each time but did not reach statistical significance compared to vehicle ($p = 0.208$ and $p = 0.296$, respectively). At the end of treatment the summary score was reduced by 2.7 points by verum and by 2.4 points by the base vehicle cream compared to baseline. Also, no statistical significant difference was seen for the individual scores for pruritus, erythema, edema/papulation, oozing/crust, excoriation and lichenification (Table 3). In a global assessment of

Table 1b. Demographics and baseline characteristics for the overall ITT-population (n = 88) and the post-hoc "temperature" subset (n = 64).

Baseline characteristics	Verum	Vehicle	P Value	Verum	Vehicle	P Value
Target area	n = 87	n = 87		n = 64	n = 64	
Summary score	7.2 ± 2.6	7.2 ± 2.6	0.785	7.7 ± 2.6	7.6 ± 2.6	0.639
Pruritus (VAS) - cm	4.0 ± 2.6	4.0 ± 2.7	0.936	nd	nd	
Erythema score	2.1 ± 0.6	2.1 ± 0.6	0.928	nd	nd	–
Edema/papulation score	1.6 ± 0.9	1.6 ± 0.9	0.970	nd	nd	–
Oozing/crust score	0.7 ± 0.9	0.7 ± 0.8	0.972	nd	nd	–
Excoriation score	1.2 ± 0.8	1.2 ± 0.9	0.867	nd	nd	–
Lichenification score	1.6 ± 0.7	1.6 ± 0.7	0.977	nd	nd	–

Values are means ± standard deviation.

Table 2. Analysis of the primary endpoint for the ITT-population (n = 88) and the post-hoc "temperature" subset (n = 64).

	Verum	Vehicle	P Value	Verum	Vehicle	P Value
Endpoints	n = 87	n = 87		n = 64	n = 64	
Summary score						
Visit 1	7.20 ± 2.61	7.17 ± 2.55		7.66 ± 2.64	7.61 ± 2.62	
Visit 2	5.09 ± 3.40	5.33 ± 3.13		5.39 ± 3.36	5.81 ± 2.97	
Visit 3	4.48 ± 3.71	4.75 ± 3.64		4.66 ± 3.72	5.39 ± 3.65	
Pre-post-difference (v2-v1)	–2.10 ± 2.52	–1.84 ± 2.59	0.208	–2.27 ± 2.58	–1.80 ± 2.51	0.134
Pre-post-difference (v3-v1)	–2.71 ± 3.48	–2.43 ± 3.26	0.296	–3.00 ± 3.57	–2.22 ± 3.23	0.019

Values are means ± standard deviation.

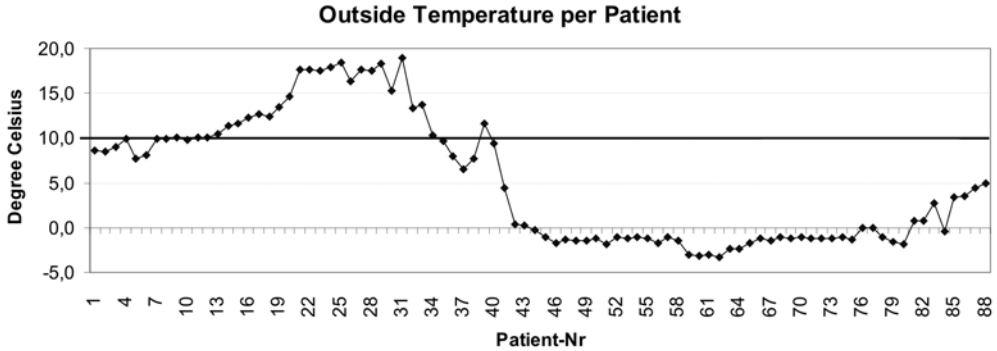

Figure 1. Mean temperature per patient and treatment duration for the ITT population (n = 88). Outside temperature was documented for every day during the enrollment and treatment phase of the trial. For every patient the mean temperature over the whole individual treatment period is plotted. For the subanalysis only those patients were included whose mean treatment temperature was 10 °C or less (cut-off line).

efficacy for verum 18.4% of patients reported no symptoms, symptoms had markedly improved in 29.9% of patients, while symptoms were unchanged in 12.6% of patients and worsened in 19.5% of patients. The corresponding numbers for vehicle are 17.2, 27.6, 6.9 and 24.1% (Figure 2a).

The recruitment phase lasted 13 months and included a cold and long winter followed by a very warm sunny summer and a mild fall.

Table 3. Analysis of secondary endpoints for the ITT-population (n = 88).

	Verum	Vehicle	P Value
Endpoints	n = 87	n = 87	
VAS pruritus/cm			
Visit 1	4.01 ± 2.60	3.96 ± 2.68	
Visit 2	2.80 ± 2.71	2.81 ± 2.82	
Visit 3	2.46 ± 2.92	2.53 ± 2.85	
Pre-post-difference (v2-v1)	–1.21 ± 29.8	–1.14 ± 2.99	0.892
Pre-post-difference (v3-v1)	–1.55 ± 3.28	–1.42 ± 3.10	0.474
Erythema			
Visit 1	2.07 ± 0.62	2.10 ± 0.65	
Visit 2	1.47 ± 0.86	1.59 ± 0.87	
Visit 3	1.32 ± 1.04	1.39 ± 0.96	
Pre-post-difference (v2-v1)	–0.60 ± 0.78	–0.52 ± 0.82	0.348
Pre-post-difference (v3-v1)	–0.75 ± 0.98	–0.71 ± 0.93	0.736
Edema/papulation			
Visit 1	1.60 ± 0.91	1.57 ± 0.95	
Visit 2	1.11 ± 0.99	1.11 ± 0.98	
Visit 3	0.95 ± 1.03	1.02 ± 0.99	
Pre-post-difference (v2-v1)	–0.48 ± 0.80	–0.46 ± 0.89	0.755
Pre-post-difference (v3-v1)	–0.64 ± 1.00	–0.55 ± 1.05	0.287
Oozing/crust			
Visit 1	0.74 ± 0.88	0.70 ± 0.84	
Visit 2	0.46 ± 0.71	0.44 ± 0.64	
Visit 3	0.46 ± 0.74	0.47 ± 0.71	
Pre-post-difference (v2-v1)	–0.28 ± 0.69	–0.26 ± 0.96	0.953
Pre-post-difference (v3-v1)	–0.28 ± 0.97	–0.23 ± 0.87	0.470
Excoriation			
Visit 1	1.16 ± 0.82	1.18 ± 0.88	
Visit 2	0.71 ± 0.91	0.80 ± 0.86	
Visit 3	0.61 ± 0.87	0.64 ± 0.85	
Pre-post-difference (v2-v1)	–0.45 ± 0.79	–0.38 ± 0.89	0.479
Pre-post-difference (v3-v1)	–0.55 ± 0.94	–0.54 ± 0.94	0.990
Lichenification			
Visit 1	1.63 ± 0.73	1.61 ± 0.70	
Visit 2	1.33 ± 0.82	1.39 ± 0.84	
Visit 3	1.14 ± 0.85	1.22 ± 0.93	
Pre-post-difference (v2-v1)	–0.30 ± 0.65	–0.22 ± 0.67	0.252
Pre-post-difference (v3-v1)	–0.49 ± 0.82	–0.39 ± 0.87	0.207

Values are means ± standard deviation.

This resulted in conditions that were not uniform across the study population regarding ambient temperature, moisture and dryness. To confirm this assertion we determined the average outside temperature during the treatment period for each individual patient. Temperature data for the local area in which the study took place were collected from an internet site of the State Department of Agriculture of the State of Bavaria with detailed climate information for each day of the trial. Figure 1 shows that the study population consisted of two very uneven groups in terms of weather conditions during treatment. In a post-hoc subanalysis we decided to exclude all patients that were treated at average outside temperatures above 10 °C. This cut allowed for the largest subpopulation possible to be analyzed within a reasonably homogeneous temperature range. Only the primary summary score was analyzed as well as the global assessment of efficacy by the patients. 64 patients of the total population of 88 patients were included in this subanalysis. Baseline characteristics of the subpopulation are shown in Figure 1 and are comparable to the overall study population. Severity of atopic dermatitis may be more pronounced in the subpopulation. After 4 weeks of treatment the summary score was reduced by 3.0 points by the study medication and by 2.2 points by vehicle alone (Table 2). This difference was statistically significant ($p = 0.019$). The global assessment of efficacy by the patients of the subpopulation shows a clear difference in the category "markedly improved" and "slightly improved" for verum vs. vehicle. Symptoms were unchanged or worsened more often in the vehicle group (Figure 2b).

Safety

The study ointment was very well tolerated. The mean of the global assessment by the patients based on a 4-point scale (0 = excellent, 1 = good, 2 = moderate, 3 = poor) was 0.36 for verum and 0.40 for vehicle after 4 weeks of treatment. The results by the physicians were 0.38 and 0.35, respectively.

A total of 33 adverse events were reported, 1 for the verum target site, 1 for the vehicle target site and 31 nontarget site adverse events. None of the nontarget site adverse events were rated by the physician as drug-related. Both target site events led to a discon-

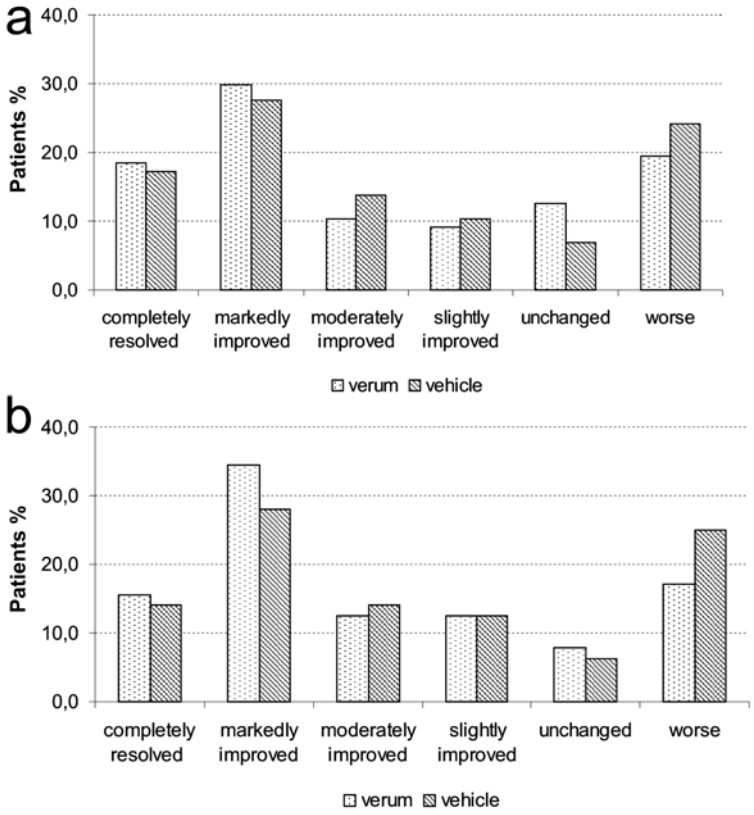

Figure 2. Global assessment of efficacy by the patients for the ITT population (n = 88) (2a) and the post-hoc "temperature" subset (n = 64) (2b): state of overall symptoms.

tinuation of the study. No serious adverse events or deaths were reported in this trial.

Discussion

A host of herbal preparations are offered for many different ailments including skin disease. Many different herbs have been studied in mostly small and dated experimental and clinical trials for various skin conditions like psoriasis, contact dermatitis, seborrheic dermatitis, acne, wound healing, herpes etc. [Bedi and Shenefelt 2002, Brown and Dattner 1998, Levin and Maibach 2002]. However, randomized controlled clinical trials with patients suffering from atopic dermatitis are limited. Borage oil and primrose oil are the best studied oral treatments for atopic dermatitis, however, with conflicting and inconclusive results. Both oils contain large quantities of γ-linolenic acid which is deficient in patients with atopic dermatitis. Most recent and well-powered placebo-controlled randomized trials have shown no beneficial effects in the case of borage oil or only small and delayed beneficial effects of primrose oil on symptoms of atopic dermatitis [Morse and Clough 2006, Takwale et al. 2003]. Data on the clinical efficacy of topical herbal creams or ointments for the treatment of atopic dermatitis are also sparse. One double-blind, randomized trial compared an hamamelis distillate with a drug-free vehicle and a 0.5% hydrocortisone cream in 72 patients with moderately severe atopic dermatitis in a half-side comparison design [Korting et al. 1995]. After 1 and 2 weeks, there was no difference between the vehicle and the hamamelis cream in the analyzed basic criteria (itching, erythema, scaling) and minor criteria (edema, papules, pustules, exudation, lichenification, excoriation and fissures). Also, hamamelis cream was less effective than 0.5% hydrocortisone. In another half-side comparison trial, a cream containing a chamomile extract was tested on patients with medium-degree atopic eczema for 2 weeks versus vehicle and versus 0.5% hydrocortisone cream [Patzelt-Wenczler and Ponce-Poschl 2000]. The chamomile cream was only marginally better than vehicle and surprisingly slightly superior to 0.5% hydrocortisone. A licorice gel was found to be more effective than placebo in 60 patients with atopic dermatitis [Saeedi et al. 2003] and a cream containing an hypericum extract was compared to vehicle in a half-side comparison trial with 21 atopic dermatitis patients [Schempp et al. 2003]. Using a modified SCORAD-index, hypericum was found to be statistically superior to vehicle after 1, 2 and 4 weeks of treatment.

Two randomized trials are published with MAS063DP (Atopiclair). Atopiclair is a non-steroidal topical agent for the treatment of atopic dermatitis and related eczemas. It contains glycyrrhetinic acid, telmesteine and an extract from vitis vinifera combined with hyaluronic acid and other components. Strictly speaking, atopiclair is not a "classic" herbal cream. In a vehicle-controlled study in 30 adult patients with mild-to-moderate AD, atopiclair improved the total body area affected, itch score and EASI score after 22 days treatment [Belloni et al. 2005]. These results were confirmed in a multicenter, randomized trial with 218 adult patients. Compared to vehicle, atopiclair was statistically superior in

all outcomes (EASI, itch, %BSA, IgA) at all time points [Abramovits et al. 2006].

MimyX cream is another nonsteroidal topical treatment for atopic dermatitis which has marketing authorization as a medical device. MimyX cream is not a herbal ointment, but will be briefly considered in this discussion. The cream contains various ingredients, mainly oils and lipids. Its main constituent is palmitoylethanolamin (PEA), a fatty acid that is deficient in atopic skin. PEA is a cannabinoid agonist and has antiinflammatory properties. No published clinical trial data of MimyX can be found in the MEDLINE database except for a small review by Abramovits and Perlmutter [2006]. In a comparative study with 18 patients MimyX cream was found to be as efficient as hydrocortisone 1% cream in the reduction of pruritus, infiltration, excoriation and lichenification. Only sparse information is given regarding study design and results.

The plant extracts of the herbal ointment used in this study have been reported to be effective for the treatment of various skin diseases including eczema with itchy and flaky skin in monographs and textbooks [Brinkhaus et al. 2000, Gieler 1993, Mezger 1985, Monographies of Kommission D, Wiesenauer 1992]. Also, two small open studies with a total of 79 children between 2 and 12 years of age have suggested that an ointment containing Mahonia aquifolium, Viola tricolor and Centella asiatica can reduce symptoms of atopic dermatitis [Abeck et al. 2005].

In the current trial we used a half-side comparison design which is an accepted and established design in dermatological trials. Reliability of and compliance by the patient is very important for this design. We believe this was achieved since the investigative center has a long history of experience in clinical trials with a pool of patients very well-used to clinical trial procedures. In addition, patients were meticulously instructed in verbal and written form and had to apply study ointments in the presence of the physician at the first visit. There was no concern of intentional mix-ups of tubes and treatment sides since patients were allowed to stop the trial at any time to receive more effective treatments.

The study ointment with Mahonia aquifolium, Viola tricolor and Centella asiatica improved all analyzed symptoms of atopic dermatitis compared to the vehicle, however, the differences were not statistically significant. One reason for this observation could be the effectiveness of the base cream alone to improve the barrier function of the skin. Another factor that could influence the outcome of eczema is the climate. It is known that sunlight, warmth and non-dry conditions will aid in healing of eczematous lesions [Vocks et al. 2001]. These conditions can be considered as confounding factors for a clinical trial with atopic dermatitis patients. In fact, recruitment and treatment lasted for 13 months with considerable differences in weather conditions, resulting in an inhomogeneous study population. It was, therefore, hypothesized that the very warm und sunny conditions would improve the skin lesions of both target sizes irrespective of the treatment. To test this assumption we decided to do a post-hoc analysis with a subgroup of patients under closely identical climate condition. The mean ambient temperature was calculated for the complete treatment duration of each individual patient. A cut was then made at the mean temperature of 10 °C to include as many patients as possible in a homogeneous subgroup regarding temperature. It should be pointed out that the cut is a mean and that some patients had also higher outside temperatures during their treatment. Under these conditions, the study ointment reached a clear statistical significance compared to the vehicle. Further cuts down to 5 °C or even to 0 °C outside temperature during treatment with the ointment did not change the results confirming the confounding nature of the sun and warm climate (data not shown).

The results of this trial suggest that an ointment with Mahonia aquifolium, Viola tricolor and Centella asiatica can improve symptoms of atopic dermatitis more effectively than base cream in cold and dry weather conditions (e.g. during the winter season). It may be assumed that patients with mild forms of dermatitis might be able to control the disease during cold weather without having to use corticosteroids. Patients under corticosteroid therapy might also benefit from the ointment in corticosteroid-free intervals. However, during warm weather, the ointment is statistically not better than a DAC base formulation. Further trials, ideally using a parallel-group design and not restricted to certain target areas, are necessary to further evaluate the efficacy

of Mahonia aquifolium, Viola tricolor and Centella asiatica in the topical treatment of mild-to-moderate atopic dermatitis.

References

Abeck D, Klövekorn W, Danesch U. Behandlung des atopischen Ekzems bei Kindern mit einer pflanzlichen Heilsalbe – Ergebnisse einer offenen Studie mit Ekzevowen derma. Akt Dermatol. 2005; *31:* 523-526.

Abramovits W, Boguniewicz M; Adult Atopiclair Study Group. A multicenter, randomized, vehicle-controlled clinical study to examine the efficacy and safety of MAS063DP (Atopiclair) in the management of mild to moderate atopic dermatitis in adults. J Drugs Dermatol. 2006; *5:* 236-244.

Abramovits W, Perlmutter A. MimyX cream. Skinmed. 2006; *5:* 29-30.

Bedi MK, Shenefelt PD. Herbal therapy in dermatology. Arch Dermatol. 2002; *138:* 232-242.

Belloni G, Pinelli S, Veraldi S. A randomised, double-blind, vehicle-controlled study to evaluate the efficacy and safety of MAS063D (Atopiclair) in the treatment of mild to moderate atopic dermatitis. Eur J Dermatol. 2005; *15:* 31-36.

Bieber T, Cork M, Ellis C, Girolomoni G, Groves R, Langley R, Luger T, Meurer M, Murrell D, Orlow S, Paller A, de Prost Y, Puig L, Ring J, Saurat JH, Schwarz T, Shear N, Stingl G, Taieb A, Thestrup-Pedersen K, Pediatric Advisory Committee of the Food and Drug Administration. Consensus statement on the safety profile of topical calcineurin inhibitors. Dermatology. 2005; *211:* 77-78.

Brinkhaus B, Lindner M, Schuppan D, Hahn EG. Chemical, pharmacological and clinical profile of the East Asian medical plant Centella asiatica. Phytomedicine. 2000; *7:* 427-448.

Brown DJ, Dattner AM. Phytotherapeutic approaches to common dermatologic conditions. Arch Dermatol. 1998; *134:* 1401-1404.

Ernst E. Are herbal medicines effective? Int J Clin Pharmacol Ther. 2004; *42:* 157-159.

Gieler U. Neue Perspektiven der Psoriasistherapie mit Mahonia-aquifolium-Therapie mit homöopathischen Externa. Dtsch Dermatol. 1993; *11:* 1201-1207.

Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980; *Suppl. 92:* 44-47.

Kolbe L, Kligman AM, Schreiner V, Stoudemayer T. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. Skin Res Technol. 2001; *7:* 73-77.

Korting HC, Schafer-Korting M, Klövekorn W, Klövekorn G, Martin C, Laux P. Comparative efficacy of hamamelis distillate and hydrocortisone cream in atopic eczema. Eur J Clin Pharmacol. 1995; *48:* 461-465.

Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. J Clin Invest. 2004; *113:* 651-657.

Levin C, Maibach H. Exploration of "alternative" and "natural" drugs in dermatology. Arch Dermatol. 2002; *138:* 207-211.

Mezger J. Gesichtete homöopathische Arzneimittellehre. Heidelberg: Karl F. Haug Verlag; 1985.

Morse NL, Clough PM. A meta-analysis of randomized, placebo-controlled clinical trials of Efamol evening primrose oil in atopic eczema. Where do we go from here in light of more recent discoveries? Curr Pharm Biotechnol. 2006; *7:* 503-524.

Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. J Allergy Clin Immunol. 2003; *112:* 128-139.

Patzelt-Wenczler R, Ponce-Poschl E. Proof of efficacy of Kamillosan® cream in atopic eczema. Eur J Med Res. 2000; *5:* 171-175.

Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol. 1989; *Suppl. 144:* 13-14.

Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. J Dermatol Treat. 2003; *14:* 153-157.

Schafer L, Kragballe K. Abnormalities in epidermal lipid metabolism in patients with atopic dermatitis. J Invest Dermatol. 1991; *96:* 10-15.

Schempp CM, Windeck T, Hezel S, Simon JC. Topical treatment of atopic dermatitis with St. John's wort cream – a randomized, placebo-controlled, double-blind half-side comparison. Phytomedicine. 2003; *Suppl. 4:* 31-37.

Takwale A, Tan E, Agarwal S, Barclay G, Ahmed I, Hotchkiss K, Thompson JR, Chapman T, Berth-Jones J. Efficacy and tolerability of borage oil in adults and children with atopic eczema: a randomised, double-blind, placebo-controlled, parallel group trial. BMJ. 2003; *327:* 1385-1388.

Vocks E, Busch R, Frohlich C, Borelli S, Mayer H, Ring J. Influence of weather and climate on subjective symptom intensity in atopic eczema. Int J Biometeorol. 2001; *45:* 27-33.

Wiesenauer M. Mahonia aquifolium-Salbe bei psoriasis vulgaris. Z Allgemeinmed. 1992; *68:* 670-674.

Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, Asher I, Beasley R, Bjorksten B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Shah J, Sibbald B, Strachan D, von Mutius E, Weiland SK. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. J Allergy Clin Immunol. 1999; *103:* 125-138.