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Short- and long-term effects of two emollients on itching and skin restoration in xerotic eczema

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Abstract
Pruritus is associated with various skin diseases, dry skin, and with it an impaired skin barrier function. The study objective was to investigate short-term and long-term effects of two emollients on symptoms and skin barrier functions in xerotic eczema. Randomized, double-blind, study enrolling females/males, with bilateral itching. Two emollients, containing lactic acid and refined almond oil with/without polidocanol were administered on left versus right body sides. Itching severity, skin moisture, lipid content, and pH were assessed on Day 1, within 30–120 min after first administration, and on Days 7 and 14, and compared with baseline assessments. Severity of itching decreased 30 min after first administration of both emollients compared with baseline ($p < .0001$) and reached a maximum reduction of 63% ($p < .0001$) and 69% ($p < .0001$) on Day 14. Skin moisture and lipid content increased after first application, and further ameliorated within 14 days of treatment ($p < .0001$). Both emollients were tolerated well, and only a few adverse events were reported. This study confirmed the clinical efficacy of the two study emollients to substantially reduce itching already after first administration, and restore skin barrier integrity and thus should be considered as therapeutic approach for xerotic eczema.

KEYWORDS
emollients, lactic acid, almond oil, itching, skin restoration, xerotic eczema

1 INTRODUCTION

Pronounced pruritus is one of the most prominent symptoms of many skin diseases such as atopic or xerotic eczema and psoriasis (AWMF-S2k, 2015; AWMF-S2k, 2016; Darsow, Pfab, Valet, Tölle, & Ring, 2012; Puschmann, Melzer, & Welzel, 2003). The clinical picture and symptoms, notably the often unbearable chronic pruritus as a major symptom of dry skin diseases, may induce severe psychological stress with a negative impact on wellbeing and daily activities (AWMF-S2k, 2015; AWMF-S2k, 2016; Puschmann et al., 2003). Medical guidelines expect a dual action from effective therapies; a quick relief of the itching during the acute phase and sustained relief during the chronic phase (AWMF-S2k, 2015; AWMF-S2k, 2016). Topical glucocorticoids reduce inflammation and itching in the acute treatment phase. However, administration of topical glucocorticoids for longer treatment periods is not recommended and limited due to the high potential of adverse events (Carr, 2013). Beside the pruritus treatment, a sustained restoration of the skin barrier by normalization of moisture and lipid contents is paramount for effective treatment (Weisshaar, 2009; Nebus, 2012).

Over recent years it became clear, that a genetic disposition toward an impaired skin barrier function is a major cause for the manifestation of dry skin diseases like atopic dermatitis. Certain genetic mutations may lead to altered compositions of essential bilayer components, which impair skin barrier integrity (Jungersted et al., 2010; McLean, 2016; Rabionet, Gorgas, & Sandhoff, 2014; Vyumvuhore, Tfayli, Manfaie, & Baillet-Guffroy, 2013). Filaggrin is essential for the regulation of epidermal homeostasis. Profilaggrin undergoes processing in the upper stratum corneum, a process during which free amino acids are released that assist in water retention and function as natural moisturizing factors (NMF) (Ovaere, Lippens, 2010; Ovaere, 2013).
Vandenabeele, & Declercq, 2009; Paloncynova, 2015). Ceramides are sphingolipids which are of major importance for the homeostasis of the stratum corneum. Among the various ceramides, it is predominantly the linoleic acid containing ceramide I, which is crucial for the stratum corneum integrity (Liu, Xia, Chen, Xue, & Zheng, 2015).

In addition, salts of lactic acid have been shown to exhibit moisturizing and barrier stabilizing effects (Sugawara, Kikuchi, Tagami, Aiba, & Sakai, 2012; Vyumvuhore et al., 2013). Lactic acid is a physiologically relevant NMF in human sweat as well as significantly rehydrates the skin when added topically (Sugawara et al., 2012). Topical treatments with a combination of moisturizing factors, such as lactic acid, plus lipophilic components, such as natural fatty oils or linoleic acid, showed clinical evidence in stabilizing the skin barrier by restoring moisture and modifying the sphingolipid bilayer in the stratum corneum (Hon, Leung, & Barankin, 2013; Jungersted et al., 2010; McLean, 2016; Rabionet et al., 2014; Van Smeden et al., 2014). Polidocanol has been used as a compound for oral mucosa preparations, in emollients to treat itching for more than 50 years, and recently in parenteral formulations for sclerotherapy (Angerer et al., 2006; Ballmer-Weber & Dummer, 2007; Berberian, Gorman, Drobeck, Coulston, & Slighter, 1965; Goldman, 1989; Matthies, 1993; Puschmann et al., 2003; Ring & Fröhlich, 1985; Siems & Soehrling, 1952; Soehring, Frahm, & Mietzko, 1952; Ständer et al., 2006).

Despite the long usage of this compound, we could only find one double-blind, placebo-controlled clinical study investigating the effects of polidocanol versus placebo on itching in healthy volunteers. The cowhage induced itching test-method showed that polidocanol reduced itching during the 30 min test period (Hawro et al., 2014). Other case and open-label studies with formulations containing polidocanol showed beneficial effects on itching, which, however, could not be attributed solely to polidocanol (Hauss, Proppe, & Matthies, 1993; Puschmann, 1992; Schöpf, 1992; Vieluf, Matthies, & Ring, 1992).

The two emollients investigated in this study have been developed for xerotic skin conditions, including atopic dermatitis. Both emollients (AL and AC) are oil-in water formulations containing lactic acid, almond oil, and a slightly different lipid content. This results in a distinctive consistency reflecting specific preferences of patients. In addition, AC contains in addition polidocanol.

The primary aim of our study was to investigate the short-term and long-term effects on itching and restoration of skin barrier functions in patients with xerotic eczema including atopic dermatitis compared with pre-treatment condition (change to baseline) for each of the two emollients.

2 | PATIENTS/METHODS

2.1 | Study design

This randomized, double-blind, two-arm intra-individual (right–left body sides), multicenter study was conducted in four dermological departments of Swiss hospitals. The Swiss Health Authority and independent Ethics Committees approved the study according to Swiss regulations. The inclusion criteria were: females and males, 18–75 years old, with sensitive or mildly inflamed (fissured, scaly) skin conditions due to xerotic eczema including atopic dermatitis, moderate to severe itching of comparable right–left severity on arms or legs, and treatments (emollients or creams) containing active substances, including but not limited to lactic acid, urea or polidocanol were not allowed for at least 3 days before the baseline visit (administration of cosmetic products was permitted). The use of cortisone or calcineurin inhibitors containing lotions, immunosuppressive drugs, retinoids, and UV-light therapy within 4 weeks prior to inclusion and during the study was prohibited.

2.2 | Study population

Patients were enrolled after signing the written informed consent. Two medicinal emollients registered in Switzerland containing lactic acid (5%) and refined almond oil (10%) rich in linoleic acid (20 to 30%) (Antidry Lotion [AL]) or lactic acid (5%), refined almond oil (10%) and in addition the antipruritic compound polidocanol (5%) (Antidry Calm [AC]) were provided in 500 mL flasks with dispenser blinded and randomized to be administered on the right versus left body side (labeling indicated administration side with “R” or “L”) twice daily. At Baseline (BL), prior to first administration of the study emollients, the extremities with the most severe bilateral itching (arms or legs) were defined as study areas. The patients were instructed to apply the study emollients twice daily (mornings and evenings). The study emollient to be used on the left arm and leg was dispensed into the right hand, and vice versa. For correct dosage, the dispenser had to be pressed two times (2.4 mL) for treatment of the arms, or three times (3.6 mL) for treatment of the legs. To confirm adherence to therapy, the weight of study flasks was determined before and after the first administration, on Days 7 and 14, respectively. Patient reported outcomes are the state-of-the-art evaluation tool to assess both, short-term and long-term effects on itching (Liu et al., 2015; Pereira & Stander, 2017; Puschmann et al., 2003). As published in Puschmann et al. (2003) and recommended in medical guidelines (AWMF-S2k, 2016), the severity of itching was assessed by a visual analogue scale (VAS) 0–100 (100 mm scale). The current itching score was recorded on Day 1, before the first administration under instruction by the study nurse and after 30, 60, 90, and 120 min, respectively. The 24 h itching score (maximal itching severity within the last 24 hours) was recorded at BL (before first administration), and on Days 7 and 14. Since restoration of epidermal barrier properties is one of the most important features to improve symptoms of dry skin diseases, measurements of skin moisture, lipid content and pH were performed at short-term and long-term intervals (Courage + Khazaka electronic GmbH, 2012; Hussain et al., 2016). Skin moisture, lipid content and pH were measured using a DERMA Unit SSC 3 device (Courage + Khazaka electronic GmbH, 2012). Clinical efficacy and tolerability evaluated by investigators and patients were assessed using a 4-point Likert Scale (0 = unsatisfactory, 1 = moderate, 2 = good, 3 = very good) (Jamieson, 2004).

2.3 | Statistical analysis

Based on study result of Puschmann et al. (2003), a sample size of 42 had 80% power to detect a difference in VAS means of 0.83 (Delta of BL versus VAS actual score[s] within 2 hr after administration of AL.
and AC compared with pre-treatment BL), assuming a standard deviation of differences of 1.67 using a paired t-test with a 0.0125 one-sided significance study area and time point (30, 60, 90, and 120 min). Data are shown as mean (∓SD). In order to compare BL and follow up data, Wilcoxon signed rank test or t-test were performed depending whether the data were normally distributed or not to calculate p-values. To compensate for estimated dropouts, 48 patients needed to be included. The current itching score was calculated as change to BL for each patient, each study area (treated with AL and AC), and each time point (30, 60, 90, and 120 min).

3 | RESULTS

Fifty patients were included at four centers between February 2015 and May 2016. At all, five patients (one screening failure, four protocol deviations [three related to low severity of itching on Day 1 and one non-compliance]) were excluded from the efficacy analysis population (EAP). Forty-five patients were included in the EAP and one premature termination was reported due to bilateral exacerbation of pruritus. The majority of patients were females (67%) and the mean age was 52 (∓18) years. The mean BL values of itching severity and skin parameters for the study areas treated with AL and AC were comparable (Figure 1 and Table 1). The 24 hr itching scores were slightly higher compared with the current itching scores (Figure 1a and b).

After the first administration of AL on Day 1, the mean current itching score decreased from 54.6 (∓15.4) at BL to 32.9 (∓22.9) already after 30 min (p < .0001), and then further decreased after 60 and 90 min, toward 24.6 (∓19.9) after 120 min (p < .0001) (Figure 1). After the first administration of AC, the mean (∓SD) current itching score decreased from 54.3 (∓15.4) at BL to 32.3 (∓22.2) after 30 min (p < .0001), continued to decrease after 60 and 90 min and dropped to 22.8 (∓21.2) after 120 min (p < .0001) (Figure 1). Two hours after first administration of AL and AC, the current itching score was reduced by 55% (p < .0001) and 58% (p < .0001), respectively. On study areas treated with AL, the mean 24 h itching score decreased from 64.6 (∓14.5) at BL to 23.4 (∓27.4) on Day 14 (p < .0001), and on those treated with AC from 63.9 (∓15.8) at BL to 19.5 (∓25.1) on Day 14 (p < .0001) (Figure 1). The mean 24 h itching scores were reduced after 14 days of twice daily administration of AL and AC by 63% (p < .0001) and 69% (p < .0001), respectively. To compare the short term effect on severity of itching between the two study emollients AL and AC, the differences from BL (∆30, ∆60, ∆90,
and \( \Delta 120 \) min, calculated as area under the curve [AUC], e.g., AUC\(_{0-30}\), AUC\(_{30-60}\), AUC\(_{60-90}\), and AUC\(_{90-120}\) were summarized as AUC\(_{0-120}\) per patient and study area. An exploratory paired t-test was performed on the EAP and revealed that the effects of AL and AC on reducing the severity of itching were very similar (\( p = .9384 \)).

Treatment with AL increased the skin moisture by 40% (\( p < .0001 \)) from 27.8 (±8.7) at BL to 39.0 (±12.2) (\( p = .0001 \)) on Day 14, and the skin lipid content increased from 0.5 (±1.1) at BL to 22.9 (±33.5) on Day 14 (\( p < .0001 \)) (Table 1). Treatment with AC increased the skin moisture by 41% (\( p < .0001 \)), from 28.1 (±9.4) at BL to 38.9 (±14.7) (\( p < .0001 \)) on Day 14, and the skin lipid content from 0.6 (±1.0) at BL to 22.6 (±33.6) on Day 14 (\( p < .0001 \)) (Table 1). The skin pH of the two study areas at BL was 5.9 (±0.8) and 6.0 (±0.7), respectively, and did not change during the 14-day treatment period with AL and AC.

Clinical efficacy evaluated by investigators (CEI) and by patients (CEP) were comparable and similar for both, AL and AC. The proportions of "good/very good" ratings ranged from 76% to 80% for CEI, and from 69% to 84% for CEP. The proportion of "very good" CEP ratings increased within 120 min after first administration of AL and AC, and further till Day 14 (Figure 2). Similarly, clinical tolerability evaluated by investigators (CTI) and by patient (CTP) were comparable for AL and AC, with proportions of "good/very good" ratings of 73 to 90% for CTI, and of 82 to 92% for CTP. The highest proportions of "very good" CTI were recorded on Day 14 (49 and 47%, respectively) and "very good" CTP on Day 7 (53 and 55%, respectively).

Recording the weight of AL and AC flasks revealed a mean weight of 551.9 (±4.5) and 559.2 (±2.5) grams, respectively, before first administration, and a consumption of 6.6 (±4.2) and 7.2 (±4.2) g, respectively, after first administration at the centers, and 72.2 (±21.7) and 73.7 (±29.1) g, respectively, on Day 7, and 158.5 (±98.9) and 142.2 (±53.3) g, respectively, on Day 14.

Six patients (12.2%) exposed to AL and AC treatment experienced seven unilateral or bilateral treatment emerged adverse reactions (TEAR). No serious TEAR was reported, and 6 out of the 7 TEARs were mild or moderate. Treatment with AL and AC resulted in six and five TEARs, respectively. The following TEAR were reported: Itching [shortly after first administration (\( n = 2 \), bilateral with AL and AC),
itching eczema (n = 1, unilateral with AL), worsening of eczema (n = 1, bilateral with AL and AC leading to premature termination on Day 7), exacerbation of pruritus (n = 2, one bilateral with AL and AC and one unilateral with AC), and contact dermatitis (n = 1, unilateral with AL).

4 | DISCUSSION

A broad range of topical emollients containing various active substances are used to treat xerotic eczema including atopic dermatitis (Nebus, 2012). Literature search revealed only a few publications investigating the effects of ammonium lactate (Rogers, Callen, Wehr, & Krochmal 1989), hyaluronic acid-based foam (Draelos, 2011), creams containing ceramides and magnesium (Draelos, 2011; Koppes et al., 2016), levomenol and/or heparin (Arenberger, Arenbergerová, Drozenová, Hladíková, & Holcová, 2011), glycerol (Breternitz, Kowatzki, Langenauer, & Elsner, 2008), or a petrolatum-based emollient (Kucharekova, Van De Kerkhof, & Van Der Valk, 2003), while many RCTs with other active substances such as corticosteroids, calcineurin inhibitors, and cyclosporine have been published (Shim et al., 2016; Hussain et al., 2016; Jensen et al., 2013; Silverberg, 2014; Ortonne et al., 2003).

Our investigation represents one of the first randomized, double-blind studies in patients assessing both, a sequential short-term (30, 60, 90, and 120 min after first administration) and a long-term (over 7 and 14 days) effectiveness of two emollients (each compared with baseline) administered in a two-arm, intra-individual (right versus left body side) approach. This represents a common practice in order to minimize individual variations of skin sensation (Jensen et al., 2013; Ortonne et al., 2003).

Here, we could demonstrate that the application of the two study emollients lead to a rapid and significant reduction of pruritus in patients with xerotic eczema and associated moderate to severe pruritus. An effect on the current itching score could already be observed within 2 hr after the first application of the emollients. The twice-daily application of the study emollients over 2 weeks resulted in a marked decrease of the 24 hr itching score.

The short- and long-term effects of both study emollients, AL and AC, on itching were similar. This raised the question on the effect of polidocanol in AC. It should be emphasized, that our study was not intended, and therefore not designed to show differences on itching between AL and AC, and by that an effect of polidocanol. As to our knowledge, randomized, double-blind, controlled (placebo or comparator) clinical trials with polidocanol in patients have not been

![FIGURE 2](image-url) Clinical efficacy of AL and AC evaluated by investigators and patients on Day 1 (120 min), Day 7, and Day 14 using a 4-point Likert scale showing proportion of “very good,” “good,” “moderate,” and “satisfactory” ratings. Efficacy Analysis Population (EAP): n = 45 on Day 1 (120 min), n = 44 on Day 7, and n = 43 on Day 14. Denominator for percentages was number EAP on Day 1 (N = 45)
conducted (AWMF-S2k, 2015). A recent study using an itch-provoking test-method in healthy volunteers showed a clear antipruritic effect of polidocanol when PAR-2 dependent itch pathways (associated with atopic dermatitis) were provoked (Hawro et al., 2014). Itching was significantly reduced within 10–24 min after administration of an aqueous polidocanol solution versus placebo (water) (Hawro et al., 2014). The effect of polidocanol seems to be rapid and transient, and therefore the effect of polidocanol could not be shown in patients with pruritus when assessed at 30 min or later. Accordingly, effects specifically attributed to polidocanol need to be further investigated in an appropriate clinical setting.

Skin moisture and lipid content of the Stratum corneum are thought to be essential for the maintenance of the skin barrier (Jensen et al., 2013). Here we show that the reduction of pruritus parallels an increase of skin moisture and lipid content. Two weeks application of AL and AC, resulted in a significant increase of skin moisture and lipid content reflecting normalization of the skin barrier function. Sebumetry measurements were conducted with a minimum interval of 4–6 hr after last administration of AL and AC, except at Day 1. This explains why the lipid content 2 hr after first administration was higher compared with the levels after multiple administrations on Days 7 and 14. Interestingly, the application of AL and AC had only a very slight effect on the pH of the skin. This observation might be due to the fact that the pH at baseline was only minimally increased. A 2-week application of the study emollients was not sufficient to completely normalize the pH. Carry-over effects from the AL-treated to the AC-treated body side seem unlikely, since patients were instructed to use the left hand for the right side treatment and vice versa.

Adherence to dose regimens is essential for the effectiveness of treatments. Controlling the flask weight throughout the study confirmed that all patients of the EAP adhered to the treatment regimen. Also, the tolerability of the study medication is an important criterion for patients’ compliance. The clinical efficacy rated by patients and investigators was positive and congruent, and more than 70% of the patients and investigators rated the effect and tolerability of AL and AC as very good or good.

Although AL and AC are tolerated very well in general, treatment related adverse effects should be monitored. One patient had to stop the application of the study emollients due a contact dermatitis. Whether the dermatitis was related to skin irritation or a contact allergy has not been assessed.

5 | CONCLUSION

This clinical trial demonstrated that emollients containing refined almond oil rich in linoleic acid and lactic acid as moisturizing factor may reduce pruritus in patients with xerotic eczema. This effect could be observed as early as 30 min after first application and was even more pronounced after twice daily application of the emollients for 2 weeks. Furthermore, the results of this study clearly demonstrated that restoration of the skin barrier function and reduction itching are tightly related to each other. Because of the excellent efficacy and tolerability profile, emollients such as AL and AC should be considered as treatment for xerotic eczema.

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CONFLICT OF INTEREST

This study had been initiated and sponsored by Merz Pharma (Schweiz) AG. Eckhart Wildi is head of Medical & Regulatory Affairs, Merz Pharma (Schweiz) AG Hegenheimermattweg 57, CH-4123 Allschwil.

ClinResearch Ltd. has been contracted by Merz Pharma (Schweiz) to plan and conduct the study. Urs E. Gasser was the Medical Writer for the protocol, related study documents and clinical study report.

Dagmar Simon, was assigned as principal coordinating investigator for this study, Stephan Nobbe, Siegfried Borelli and Omar Hasan-Ali were principle investigators at the other participating sites, and Mirjam Nägeli, Pascale Kränzlin, Michael Kunz were co-investigators.

All authors have no conflict of interest relevant to the content of the submission.

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