CORONEL RAPPORTAGE 15-03

EFFICACY OF A CREAM CONTAINING CERAMIDES AND MAGNESIUM IN THE TREATMENT OF MILD TO MODERATE ATOPIC DERMATITIS: A RANDOMIZED, DOUBLE-BLIND, EMOLLIENT- AND HYDROCORTISONE-CONTROLLED TRIAL

S.A. KOPPES, S. KEZIC

Formulier Eindrapportage

De medisch ethische toetsingscommissie (METC) van het AMC wil van al het door haar beoordeelde onderzoek gemeld zien dat het onderzoek (voortijdig) beëindigd is. Heeft u als verrichter een onderzoek laten toetsen door de METC AMC? Dan bent u verplicht dit formulier na beëindiging van het onderzoek in te dienen. Met beëindiging van het onderzoek wordt bedoeld dat de laatste meting bij de laatste proefpersoon is uitgevoerd. U kunt hiervoor dit formulier Eindrapportage gebruiken en naar de METC AMC sturen, via indienenmetc@amc.nl. Mocht daar aanleiding voor zijn, dan zal de METC AMC om een uitgebreidere rapportage vragen.

U hoeft dit formulier dus alleen in te dienen bij door de METC AMC beoordeeld onderzoek.

Is uw onderzoek beoordeeld door een andere erkende METC of de ccmo?

Informeert u bij de betreffende METC of de ccmo naar de eisen ten aanzien van het melden (voortijdig) beëindiging studie.

1. Opdrachtgever van het onderzoek (verrichter volgens WMO):
   Bedrijf/organisatie: Coronel int. AMC

   Afdeling: Coronel inst.

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2. Titel van het onderzoek:
   Efficacy of a skin barrier repair cream (dermalex eczema) in atopic dermatitis patients

3. ABR protocol nummer:
   48640

4. METC AMC l nummer:
   2014-090

5. Wat is de einddatum van het onderzoek?
   06-04-2015

6. Is het onderzoek voortijdig beëindigd?
   ja ☐ nee ☒

   Zo ja, wat is hiervan de reden?

7. Op welke datum is de eerste proefpersoon geïncludeerd voor het onderzoek?
   22-sept 2014

8. Hoeveel proefpersonen zijn er in totaal (wereldwijd) geïncludeerd?
   100

9. Hoeveel proefpersonen zijn er in totaal in Nederland geïncludeerd?
   100

10. Indien multicenter-onderzoek, hoeveel proefpersonen zijn er per centrum in Nederland geïncludeerd?
    (*door na elke ingevoerd persoon de enter toets te gebruiken ontstaat een opsomming van de centra/aantal proefpersonen*)
    Centrum/aantal proefpersonen
    0

11. Hoeveel proefpersonen in Nederland hebben het onderzoek volledig doorlopen?
    (Bij open/single blind interventieonderzoek aangeven hoeveel proefpersonen per groep)

    (*door na elke ingevoerde Groep/aantal proefpersonen de enter toets te gebruiken ontstaat een opsomming van de groepen/aantal proefpersonen*)

    Groep/aantal proefpersonen

    95

12. Zijn er publicaties/abstracts over de resultaten van het onderzoek verschenen?
ja ☐ nee ☒

Indien ja, deze svp bijvoegen.

Ps: artikel is ‘under submission’

13. Is er een eindrapportage met resultaten en conclusies van het onderzoek beschikbaar?
ja ☐ nee ☒

Indien ja, deze svp bijvoegen.

Indien neen, dan wil de METC deze graag binnen 1 jaar na einddatum onderzoek ontvangen.

.

Dit formulier is naar waarheid ingevuld en een eindrapportage met resultaten en conclusies van het onderzoek.is bijgesloten

Naam hoofdonderzoeker AMC of contactpersoon verrichter: S. Kezic

EFFICACY OF A CREAM CONTAINING CERAMIDES AND MAGNESIUM IN THE TREATMENT OF MILD TO MODERATE ATOPIC DERMATITIS: A RANDOMIZED, DOUBLE-BLIND, EMOLLIENT- AND HYDROCORTISONE-CONTROLLED TRIAL

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Conflict of interest disclosures

S. A. Koppes has been reimbursed by Omega Pharma for international conference attendance.

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ABSTRACT

This RCT aimed to assess the efficacy of a cream containing ceramides and magnesium (Cer-Mg) in the treatment of mild to moderate AD and to compare it with hydrocortisone (HC) and a commonly used emollient (EM) (unguentum leniens). One-hundred patients randomized into two groups were treated for 6 weeks simultaneously (left *vs.* right body side) with either Cer-Mg and HC (Group I) or Cer-Mg and EM (Group II). The primary outcome was a reduction in severity of lesions as assessed by (local) SCORAD. Next, trans-epidermal water loss (TEWL), skin hydration, natural moisturizing factors (NMF) levels were measured. After 6 weeks, Cer-Mg and HC showed comparable significant improvement in SCORAD and TEWL while in Group II, decrease in SCORAD and TEWL was significantly greater after Cer-Mg compared to EM. Finally Cer-Mg cream showed to be more effective in improving skin hydration and maintenance of NMF levels than HC and EM.

Keywords:
Atopic dermatitis, skin barrier, ceramides, magnesium, RCT, Dermalex

INTRODUCTION

Atopic dermatitis (AD), a chronic, inflammatory skin disease characterized by dry, pruritic and erythematous skin affects up to 10 percent of adults and up to 20 percent of children in the Western world [1-3]. Patients with mild to moderate AD are constrained for long periods to over-the-counter (OTC) emollients or in some countries such as the UK and the USA to low potency-corticosteroids. However, long-term use of corticosteroids is associated with adverse side effects such as skin atrophy [4]. Such side effects are well known among the general public and (not always justifiable) anxiety about corticosteroids is a major factor in poor adherence to therapy [5-8]. Therefore, emollient therapy is often preferred by patients and is shown to significantly reduce corticosteroid use [9]. Generally, emollients aim to prevent water loss from the skin, e.g. by occlusion (petrolatum) or by addition of hygroscopic compounds (e.g. glycerol and urea) and lipids (e.g. ceramides). Identification of an inherited deficiency of the epidermal protein filaggrin as a major risk factor for AD, points to the importance of the skin barrier in the etiology of AD [10-12]. The barrier is mainly located in the stratum corneum (SC) which is composed of corneocytes surrounded by lipid lamellae composed of ceramides, cholesterol and free fatty acids [13-15]. Although emollients are regarded as basic therapy by the European Task Force on Atopic Dermatitis/EADV Eczema Task Force, their efficacy in randomized controlled trials (RCT) has been insufficiently investigated [16-20]. Therefore, the aim of the present double-blinded RCT was to assess the efficacy of an emollient which contains ceramides and magnesium (Cer-Mg), compounds involved in the maintenance of the skin barrier [21]. SC ceramide composition is altered in AD and reduced levels of ceramides and changes in their relative composition have been shown to correlate with the transepidermal water loss (TEWL) [12]. The role of magnesium in AD is relatively unknown, however, bathing in magnesium rich water showed a beneficial effect on the skin barrier in dry atopic skin [22]. Furthermore, Mg is known to be involved in ceramide synthesis, regulation of epidermal proliferation and differentiation. Additionally, children with AD showed a reduced level of serum magnesium [23, 24]. Although there is some evidence that both ceramides and magnesium might improve barrier function in AD, their efficacy still has to be elucidated preferably in randomised control trials. In the present study the efficacy of the Cer-Mg cream has been compared side-by-side with two other creams, which are frequently used in treatment of

mild and moderate AD: a low-potency topical corticosteroid (hydrocortisone acetate 1% in petrolatum-cetomacrogol) and a commonly used OTC emollient, unguentum leniens (EM).

MATERIALS AND METHODS

TRIAL POPULATION

One hundred patients were recruited from the outpatient clinic at VU University Medical Center Amsterdam (VUmc). Inclusion criteria were: (1) clinically diagnosed AD conforming to the Hanifin and Raijka criteria [25],(2) mild to moderate AD, (3) age 18 to 70 years, (4) at least two symmetrical (i.e. left and right side of the body) skin sites with comparable AD severity. The exclusion criteria were: (1) extensive UV exposure in the last 14 days and/or expected exposure during the study, (2) skin disease other than AD, (3) use of antibiotics prior (at least 4 weeks) to the study and/or expected use during the study, (4) use of systemic immuno-suppressing drugs prior (at least 4 weeks) to the study and/or expected use during the study, (5) severe disorders within the last 6 months, (6) investigator's uncertainty about the willingness or ability of the patient to comply with the protocol requirements (e.g. mental disability). In the case of adverse health effects like allergic reaction or severe deterioration of the symptoms, patients were prevented from further participation. Patients could not use any AD medication for at least 2 weeks prior to participation (wash-out period). The study was approved by the Medical Ethical Committee of the Academic Medical Centre and VUmc. All patients gave their written informed consent prior to participation.

INTERVENTION

Patients were randomly allocated into two groups. Group I was treated with Cer-Mg cream on a lesion on one side of the body and simultaneously with HC on a lesion on the contralateral side. Group II was treated simultaneously with Cer-Mg and EM contralaterally. Patients were instructed to apply one fingertip unit (approximately 1 gram) of both creams twice daily for 6 weeks. Patients were instructed not to apply cream on the morning of measurements. Furthermore, patients were asked not to apply any other product on other lesions, except the study creams. Measurements were performed under the same climate conditions (21 °C, controlled humidity) between September and January, by one investigator

(SAK). In weeks 0, 3 and 6 the parameters were measured and samples of the SC were collected for analysis. A flow diagram is given in Fig. 1.

STUDY MATERIAL

The Cer-Mg cream (Dermalex™ Eczema, Omega Pharma, Nazareth, Belgium) contained: water, ceramide 1 (0.001 %), ceramide 3 (1%), ceramide 6 II (0.5%), phytosphingosine, cholesterol, magnesium chloride hexahydrate, zeolite (the combination of magnesium and zeolites are trademarked as MagneoLite™), glycerol, cocoglycerides, cetyl alcohol, isopropyl myristate, emulsifiers and preservatives. The control products; hydrocortisone acetate 1% in petrolatum-cetomacrogol (HC) and unguentum leniens (EM, also called cold cream, consists of arachis oil, purified water, white beewax and glyceryl monooleate) both produced by Fagron, NL, BF (Capelle aan den IJssel, the Netherlands) were, together with the Cer-Mg, packed in blinded tubes by Thiopharma (Maassluis, the Netherlands) according to the GMP guidelines. The total lipid content of the Cer-Mg cream was 30%, of the EM 75% and the HC 49%.

CLINICAL PARAMETERS (PRIMARY OUTCOME)

The primary outcome of the study was the comparison of the treatments based on the change in symptom severity as assessed by the difference in the SCORAD at 3 and 6 weeks from baseline. SCORAD is based on the total body surface area affected by a disease and visually apparent symptoms (erythema, edema, excoriation, oozing/crusts, lichenification, dryness) and on two subjective parameters (pruritus and sleep deprivation, both measured on a visual analogue scale) [16]. Due to the split-body study design a modified SCORAD (local SCORAD) was used [26]. By local SCORAD, the scoring parameters were performed on the investigated skin sites and the body surface area was set to 1%.

BIOPHYSICAL PARAMETERS AND NMF (SECONDARY OUTCOMES)

The biophysical parameters included TEWL, skin surface pH and erythema. The measurements were conducted within a time period of 60 minutes at each visit under controlled environmental conditions. TEWL was measured using a Tewameter 300 (Courage and Khazaka Electronic GmbH, Cologne, Germany) [27]. Hydration was measured using a Moisture Meter SC Compact (Delfin, Inc, Kuopio, Finland). Skin pH was measured by a skin

pH meter (pH900, Courage and Khazaka Electronic GmbH, Cologne, Germany) and erythema by an erythema meter (DermaSpectrometer; Cortex Technology, Hadsund, Denmark).

NMF IN THE STRATUM CORNEUM (SC)

The SC samples were collected with an adhesive tape (3.8 cm^2, D-Squame, CuDerm, Dallas, Texas, USA) as described previously [12] and analyzed for NMF by HPLC-UV [22, 28].

STATISTICS

Sample size was calculated using power analysis (nQuery advisor). Based on data from our pilot study (unpublished, results available on request) a difference of 5 AU (SD: 4.0) on the SCORAD index could be detected in a population of 39 patients (power 80%). Anticipating a drop-out percentage of 20%, we included 50 patients per group. Data analysis was performed using IBM SPSS Statistics® version 20.0. The Shapiro-Wilk test was used to check for data normality. The differences within the investigated parameters or between the two treatments were tested by a paired student t-test (normally distributed data, data are shown as the mean value and SEM) or a Wilcoxon signed-rank test (non-normally distributed data, data are shown as the median value with interquartile ranges). A per-protocol analysis was performed as described in the study protocol.

ONLINE SUPPLEMENT CONTAINS ADDITIONAL INFORMATION ON:

PATIENTS EXPERIENCE QUESTIONNAIRE (S1, METHODS)

REGISTRATION AND MEDICAL ETHICAL APPROVAL (S1, METHODS)

RANDOMIZATION AND BLINDING (S1, METHODS)

Results

Of 100 patients recruited between October and December 2014, 95 completed the study according to the protocol. Patient characteristics are shown in supplement (S2, Results). Five patients were excluded during the study because of an allergic reaction to EM (n=2), severe worsening of eczema symptoms (n=1) or non-compliance with the study protocol (n=2) (see Fig. 1). Due to technical failure, no reliable measurements of erythema by DermaSpectrometer could be performed, however visual erythema was measured as a part of the SCORAD index. Furthermore, the measurement of proteins on the tapes from three subjects in Group II could not be performed and thus the levels of NMF in those individuals could not be determined. As the main outcome is the difference in parameter change between two treatments (e.g. Cer-Mg vs. HC in Group I and Cer-Mg vs. EM in Group II), the results will be presented separately for each group.

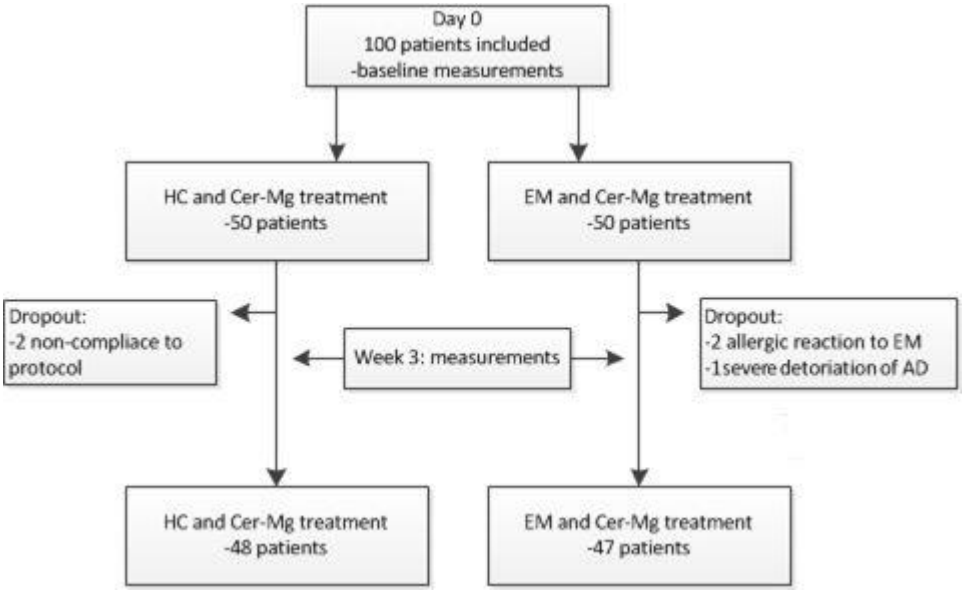

Fig. 1. Randomization flow diagram.

SCORAD

At baseline, there was no significant difference in the (local) SCORAD between the two treated skin sites in either arm of the study.

Group I: HC vs. Cer-Mg

Both treatments led to clinical improvement in the test areas, as evidenced by a significant decrease in local SCORAD after week 3 and week 6 (Fig. 2). The reduction of SCORAD from baseline (ΔSCORAD) was significantly greater for HC as compared to Mg-Cer at 3 weeks, however after 6 weeks there was no significant difference in ΔSCORAD between HC and Cer-Mg (**Fout! Verwijzingsbron niet gevonden.**). At week 6, the ΔSCORAD amounted to -11.5 (IQR: -17.4; -5.6) for HC and -9.0 (IQR:-15.9; -5.6) for Cer-Mg.

Group II: EM vs. Cer-Mg

Cer-Mg treatment led to a significantly greater decrease of SCORAD from baseline (ΔSCORAD) as compared to EM at both week 3 and week 6 (Table 2). At week 6, the ΔSCORAD was -3.5 (IQR: -10.5; 3.0) for EM and -6.7 (IQR:-14.5; -2.0) for Cer-Mg.

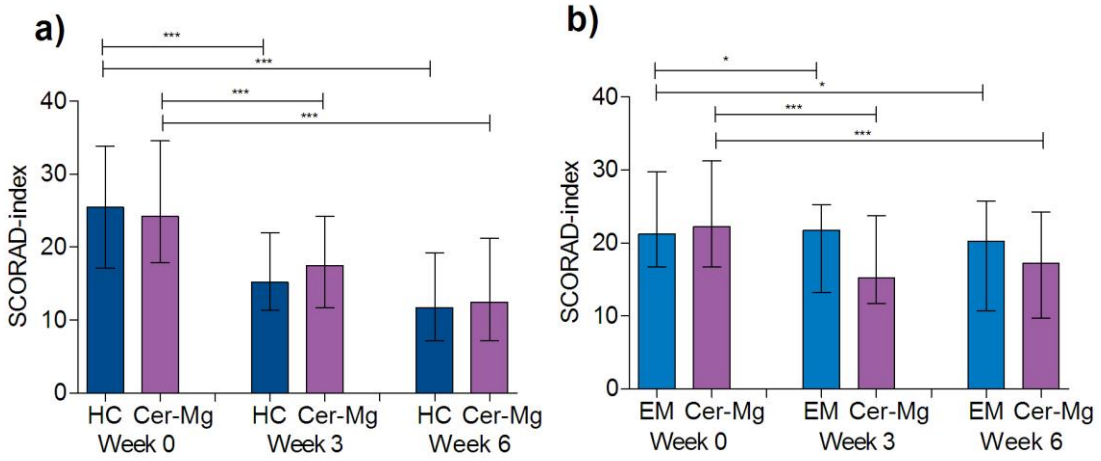

Fig. 2. Local SCORAD at baseline, after 3 and 6 weeks of treatment in Group I (HC vs Cer-Mg; n=48) and Group II (EM vs Cer-Mg; n=47). Results are shown as medians and interquartile ranges. Significance levels as tested by Wilcoxon signed-rank test: * P<0.05; ***P<0.001 .

287 Table 1. Change from baseline of clinical and biophysical parameters in the treatment Group I (Cer-Mg vs. HC).

		Group I: Cer-Mg versus HC				
		Cer-Mg	**IQR**	**HC**	**IQR**	**p-value[1]**
ΔSCORAD	Week 3	-6,25	(-8,40; -1)	-7,75	(-15,38; -3,63)	**0,0078**
(AU[2])	Week 6	-9,00	(-15,93; -5,63)	-11.5	(-17,38; -5,63)	0,1037
ΔPruritus	Week 3	-1,00	(-2; 0)	-1,00	(-4; 0)	**0,0104**
(AU)	Week 6	-2,00	(-4; 0)	-2,00	(-4; 0)	0,6123
ΔTEWL	Week 3	-4,75	(-13,66; 1,473)	-7,24	(-15,70; 2,21)	0,104
(g/m²/h)	Week 6	-6,28	(-12,20; 5,15)	-5,19	(-14,36; 2,21)	0,083
ΔHydration	Week 3	6,95	(0,23; 20,03)	3,90	(-1,2; 13,7)	**0,0202**
(AU)	Week 6	6,75	(0,83; 17,28)	3,85	(-2,9; 11,23)	**0,0183**
ΔNMF	Week 3	0,01	(-0,15; 0,23)	-0,02	(-0,18; 0,15)	0,209
(nmol/ug protein)	Week 6	0,08	(-0,12; 0,25)	-0,10	(-0,23; 0,06)	**0,0015**
ΔpH	Week 3	0,00	(-0,20; 0,28)	0,00	(-0,28; 0,40)	0,2475
	Week 6	0,00	(-0,40; 0,20)	0,10	(-0,30; 0,40)	**0,024**

288 [1]P-significance level of the difference in changes from baseline between two treatments (Wilcoxon signed-rank
289 test) ; [2]Arbitrary unit

290

291 Table 2. Change from baseline of clinical and biophysical parameters in the treatment Group II (Cer-Mg vs. EM).

		Group II: Cer-Mg versus Emollients				
		Cer-MG	**IQR**	**EM**	**IQR**	**p-value[1]**
ΔSCORAD	Week 3	-8,50	(-11,5; -1,5)	-3,50	(-8; 1)	**0,0058**
(AU[2])	Week 6	-6,70	(-14,5; -2)	-3,50	(-10,5; 3)	**0,0056**
ΔPruritus	Week 3	-1,00	(-2; 0)	0,00	(-1; 1)	**0,0173**
(AU)	Week 6	-2,00	(-3; 0)	0,00	(-2; 1)	**0,0166**
ΔTEWL	Week 3	-3,48	(-8,24; 3,66)	2,75	(-3,68; 10,07)	**0,005**
(g/m²/h)	Week 6	-3,19	(-8,57; 3,34)	4,94	(-6,97; 12,94)	**0,0208**
ΔHydration	Week 3	3,10	(-3,1; 9,6)	1,20	(-3,2; 6,5)	**0,0401**
(AU)	Week 6	9,70	(-0,7; 18,6)	1,70	(-1,5; 8,4)	0,0625
ΔNMF	Week 3	-0,02	(-0,19; 0,10)	-0,07	(-0,20; 0,09)	0,9767
(nmol/ug protein)	Week 6	-0,02	(-0,27; 0,21)	0,01	(-0,17; 0,24)	0,9767
ΔpH	Week 3	0,30	(-0,1; 0,5)	0,10	(-0,1; 0,3)	0,5189
	Week 6	0,00	(-0,2; 0,3)	0,00	(-0,3; 0,3)	0,4739

292 [1]P-significance level of the difference in changes from baseline between two treatments (Wilcoxon signed-rank
293 test) ; [2]Arbitrary units

294

LOCAL PRURITUS (ITCH) INTENSITY

Results on Pruritus show a similar pattern as the SCORAD results; an extensive description can be found in the online supplement (S2, Results).

TEWL AS A MARKER OF SKIN BARRIER

Group I: HC vs. Cer-Mg

The TEWL levels after both Cer-Mg and HC decreased significantly as compared to their corresponding baseline values (Fig. 3) reflecting an improvement of the skin barrier. The decrease in TEWL from baseline (ΔTEWL) after HC and Cer-Mg was comparable and did not significantly differ at both measurement points (**Fout! Verwijzingsbron niet gevonden.**).

Group II: EM vs. Cer-Mg

The Cer-Mg treatment did not lead to a significant change in the TEWL from baseline (Fig. 3) while the EM treatment showed a significant increase in TEWL at 3 weeks. The change in TEWL from baseline (ΔTEWL) was significantly greater after EM as compared to Cer-Mg at both time points (Table 2).

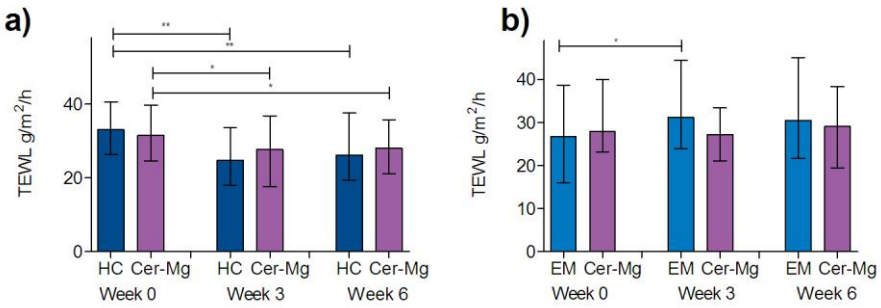

Fig. 3. TEWL at baseline, after 3 and 6 weeks of treatment in a) Group I (HC vs Cer-Mg; n=48) and b) Group II (EM vs Cer-Mg; n=47). Results are shown as medians and interquartile ranges. Significance levels as tested by Wilcoxon signed-rank test: * P<0.05; **P< 0.01;

HYDRATION

Group I: HC vs. Cer-Mg

Treatment with HC and Cer-Mg significantly improved skin hydration (Fig. 4). The increase in hydration from baseline (ΔHydration) after Cer-Mg was significantly greater after Cer-Mg as compared to HC at week 3 and 6 (**Fout! Verwijzingsbron niet gevonden.**).

Group II: EM vs. Cer-Mg

Hydration after Cer-Mg was significantly higher than the baseline values at week 3 and 6 (Fig. 4) while hydration after EM treatment improved significantly only after six weeks. The changes in hydration from baseline (ΔHydration) were significantly larger after Cer-Mg as compared to EM at week 3 (Table 2).

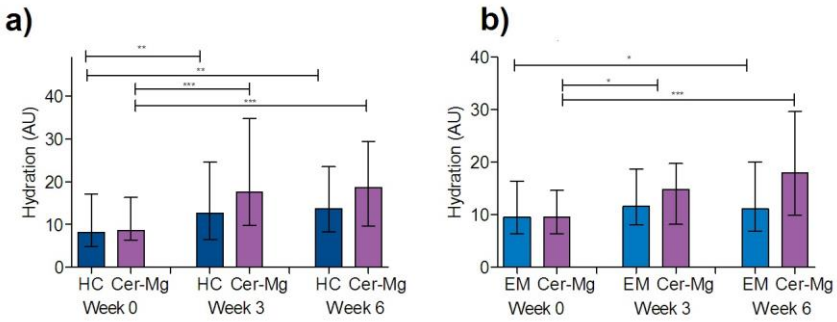

Fig. 4. Hydration at baseline, after 3 and 6 weeks of treatment in a) Group I (HC vs Cer-Mg; n=48) and b) Group II (EM vs Cer-Mg; n=47). Results are shown as the medians and interquartile ranges. Significance levels as tested by Wilcoxon signed-rank test: * P<0.05; **P< 0.01; ***P<0.001.

NMF LEVELS

Group I: HC vs. Cer-Mg

Treatment with Cer-Mg showed a tendency of NMF increase (P=0.09) (Fig. 5). In contrast to Cer-Mg, treatment with HC resulted in a significant decrease (by 22%) of NMF levels after six weeks. The difference in NMF change from the baseline (ΔNMF) between HC and Cer-Mg emollient was significant at week 6 (P<0.05), (**Fout! Verwijzingsbron niet gevonden.**).

Group II: EM vs. Cer-Mg

EM treatment showed a significant decrease in NMF at week 3 (Fig. 5). Treatment with Cer-Mg did not influence NMF levels. No significant difference in ΔNMF could be detected between the two treatments (Table 2).

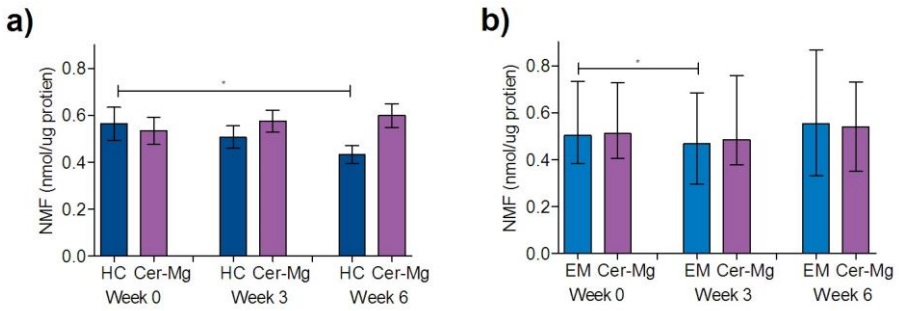

Fig. 5. NMF at baseline, after 3 and 6 weeks of treatment in a) Group I (HC vs Cer-Mg; n=48) and b) Group II (EM vs Cer-Mg; n=47). Results are shown as the medians and interquartile ranges. Significance levels as tested by Wilcoxon signed-rank test:* P<0.05.

SKIN SURFACE PH

An extensive description of pH results can be found in the supplementary file (S2, Results).

ONLINE SUPPLEMENT CONTAINS ADDITIONAL INFORMATION ON:

PATIENT CHARACTERISTICS (S2, RESULTS)

LOCAL PRURITUS (ITCH) INTENSITY (S2, RESULTS)

SKIN SURFACE PH (S2, RESULTS)

TOLERABILITY AND SUBJECTIVE PREFERENCE (S2, RESULTS)

DISCUSSION

The results of the presents study show that the Cer-Mg cream is an effective approach in improving clinical symptoms and the skin barrier. Although all three treatments led to significant improvement of clinical symptoms after six weeks, only HC and Cer-Mg cream reduced SCORAD for more than 8.7 units, which is considered clinically relevant [26]. After 3 weeks of treatment HC showed slightly but significantly greater reduction of SCORAD than Cer-Mg (-7.8 vs 6,3) while Cer-Mg showed significantly greater reduction than EM (-8.5 vs -3.5). The subjective VAS-pruritus scale and the skin barrier function parameter TEWL showed similar results: Cer-Mg and HC showed a significantly beneficial effect, which was, however, not observed after EM treatment. Overall subjective preference slightly favored the Cer-Mg which might be of importance in patients' adherence to therapy. Topical corticosteroids (TCS) are the first-line treatment of AD, however their long-term use can lead to the deterioration of the skin barrier, which is an important etiological factor in AD. Moreover, a recent study has shown that therapy with a potent TCS leads to a reduction in NMF levels which play an important role in skin hydration, antimicrobial defense and skin inflammatory status [29, 30]. This study shows for the first time that even HC which is a low-potency corticosteroid, leads to a significant reduction of NMF. Decrease in NMF has also been observed after EM treatment at three weeks, while Cer-Mg showed a tendency to increase NMF. This emphasizes the importance of this adverse side effect of HC, as reduced NMF levels may contribute to the recurrent flares. The greatest improvement in SC hydration was

observed after Cer-Mg cream that, similarly to HC, showed a decrease in TEWL but in contrast to HC had no negative effect on NMF levels.

The Cer-Mg cream contains two components which might beneficially influence the skin barrier: ceramides (1, 3 and 6 II) and a complex of magnesium and zeolites [31]. Huang et al. have shown that topical application of ceramide 1 and 3 reduces TEWL and increases hydration in SLS-irritated skin, thus beneficial effect of these ceramides, which are also present in Cer-Mg cream, might have occurred also in AD patients in the present study [32]. As the molecular size of the skin ceramides is >500 Da, which is proposed as a molecular size cut-off for percutaneous penetration [33], the question arises whether and to which extent each of individual ceramides can penetrate across the SC realizing that not only the amount but also their balance is crucial for the skin barrier. Recently, Zhang et al. demonstrated that topically applied ceramides are mainly located in the SC glyphs and that the penetration into the lipid layers is minimal [34]. It is likely that penetration of ceramides through the impaired skin barrier in AD is enhanced, however at present data on penetration of various ceramides and their efficacy in improvement of the skin barrier in AD from RCT studies is lacking.

Another rationale candidate to explain the effectiveness of Cer-Mg cream is magnesium, which is known to be involved in ceramide synthesis [23]. Topical treatments with magnesium-rich Dead Sea salts showed a beneficial effect in dry and pruritic dermatoses[27]. Whether the effect of the Cer-Mg cream could be assigned to the presence of ceramides or magnesium still has to be elucidated in a vehicle-controlled trial as some constituents of the vehicle in the Cer-Mg cream such as glycerol are known to also lead to improvement of the skin barrier [35, 36].

STRENGTHS AND LIMITATIONS

In this RCT the efficacy of Cer-Mg cream was compared with that of two currently used therapeutic options for mild to moderate AD. In most RCT's the efficacy is compared only to either corticosteroid or OTC emollient. Double-blind, split-body design offers a well-paired comparison between two treatments compensating partly for heterogeneity of disease severity among AD patients. The inclusion of biophysical and biochemical parameters provide more insight into the target of the treatment [37]. This study did not account for the spontaneous resolution of the disease over the study period. However, as the primary aim

was to compare the efficacy of Cer-Mg to the upper (HC) and lower spectrum of recommended OTC therapy for mild to moderate AD we did not include untreated site. Finally, the study does not provide insight into the working mechanism of Cer-Mg, which needs to be confirmed in the separate vehicle-controlled clinical trial.

CONCLUSIONS

The present study shows that after 6 weeks of treatment, Cer-Mg cream offers benefits over high lipid-OTC emollients and comparable clinical efficacy to HC. Additionally, in contrast to HC, it does not influence negatively the NMF concentration. Cer-Mg may therefore offer a non-steroid alternative for the treatment of mild to moderate AD. Furthermore, the fact that Cer-Mg might be used as a stand-alone treatment of mild and moderate AD as well as a maintenance therapy might improve adherence to AD-therapy.

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