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Evaluation of efficacy of a skin lipid mixture in patients with irritant contact dermatitis, allergic contact dermatitis or atopic dermatitis: a multicenter study

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Disturbances of skin barrier function occur in several skin diseases, e.g., atopic dermatitis (AD), irritant/allergic contact dermatitis (ICD, ACD). Skin barrier damage triggers the production of cytokines that stimulate lipogenesis which may also cause inflammatory processes. The aim of this study was to evaluate the efficacy of a topical skin lipid mixture in the treatment of ICD, ACD and AD. 580 consecutive patients suffering from ICD, ACD or AD were treated with a skin lipid mixture containing ceramide-3 and patented nanoparticles. Patients received the lipid mixture alone or in combination with topical corticosteroids until clearance or for 8 weeks. Both treatment groups statistically improved all parameters considered at week 4 and 8 as compared to baseline. Between the 2 treatment groups, there was a statistically significant difference in favour of combined therapy for (ICD, ACD, AD, respectively): erythema, pruritus and overall disease severity; erythema and pruritus; erythema, pruritus, fissuring and overall disease severity. No statistically significant difference was found for (ICD, ACD, AD, respectively): dryness, scaling and fissuring; scaling, fissuring and overall disease severity; dryness and scaling. Between the 2 ACD treatment groups, there was a statistically significant difference in favour of the skin lipid mixture for dryness. In conclusion, the study shows that balanced lipid mixtures are effective in improving barrier properties and the clinical condition of the skin in contact dermatitis.

Key words: barrier function; allergic contact dermatitis; stratum corneum intercellular lipids; atopic dermatitis; irritant contact dermatitis.

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The cutaneous permeability barrier, localized in the stratum corneum (SC) interstices, is constituted by lamellar bilayers, rich in cholesterol, free fatty acids and ceramides (1–4). Topical treatment with either an organic solvent, acetone, detergents or other irritants, disrupts this barrier by removal of these lipids (2–5). In response to barrier disruption, a homeostatic repair response is initiated within the nucleated epidermis, which results in the rapid restoration of lipids in the SC and normalization of barrier function; this homeostatic response includes an increase in epidermal synthesis of all 3 of the above-mentioned skin lipid classes (6–8). The requirement for an increase in lipid synthesis for barrier repair is shown by the observation that inhibition of either cholesterol, fatty acid or sphingolipid synthesis alone, leads to a delay in barrier repair (9–11). Thus, lipid production in the nucleated layers of the epidermis provides the lipids required for barrier restoration.

Recent studies have shown that application of any 1 or 2 of these lipid classes to damaged skin impedes rather than facilitates the rate of barrier repair, as can be detected by transepidermal water loss (TEWL) (11). In contrast, when members of all 3 key lipid classes are supplied together, normal rates of barrier repair occur. Furthermore, following acute barrier disruption, exogenous physiologic lipids, whether in complete or incomplete mixtures, quickly permeate the SC, are taken up by the nucleated layers of the epidermis, and are incorporated into lamellar bodies (LB).

Then, depending on the lipid composition and proportion, normal or abnormal LB are formed,

Table 1. Sex and age profiles of the patients participating to the study

Variable	Skin lipid mixture	Combined therapy
sex (M/F), ACD group	11/24	61/104
age, ACD group	36.8±9.18	35.7±12.7
sex (M/F), ICD group	34/89	64/90
age, ICD group	38.2±13.9	38.5±14.7
sex (M/F), AD group	13/11	33/32
age, AD group	31.4±11.1	27.3±11.6

Table 2. Number patients/disease and corresponding assigned treatment

Treatment groups	ACD	ICD	AD
missing	5	6	2
skin lipid mixture	35	123	24
combined therapy	166	154	65
total patients/disease	206	283	91
total patients		580	

leading to the formation of either normal or abnormal lamellar unit structures in the SC interstices (11, 12).

The present study was designed to evaluate the efficacy of a skin lipid mixture in the treatment of conditions involving barrier damage, such as atopic dermatitis (AD), and irritant/allergic contact dermatitis (ICD, ACD).

Materials and Methods

580 consecutive patients (206 with ACD, 283 with ICD and 91 with AD) entered the study (Table 1). Patients were divided into 2 treatment groups: skin lipid mixture alone and skin lipid mixture plus topical corticosteroids. 13 patients (5 with ACD, 6 with ICD and 2 with AD) were excluded from statistical analysis due to missing assigned treatment group.

All patients were treated with a skin lipid mixture containing ceramide-3, cholesterol, palmitic acid and oleic acid in a water-in-oil vehicle containing a patented nanoparticles technology (Repositol®/Alfason® Repair/Locobase Repair®/Nouriva™ Repair; Yamanouchi). The product was topically applied 1–2× a day, alone (group A) or in combination with topical corticosteroids (e.g., hydrocortisone-17-butyrate, betamethasone-valerate, prednicarbate, desoxymethasone, mometasone-furoate, prednisolone-aceponate, budesonide) (group B). The different topical corticosteroid preparations were selected in the centers participating to the study on the basis of the clinical severity of symptoms. The skin lipid mixture was applied until healing occurred or for a maximum period of 8 weeks. Dermatologists randomly assigned the patient to single or combined therapy. The severity of skin lesions was evaluated at baseline and after 4 and 8 weeks. The following symptoms were evaluated: dryness, scaling, erythema, pruritus, fissuring and overall disease severity, using a visual 4-score rating scale (0=none, 1=mild, 2=moderate, 3=severe).

Statistical analysis

All data were summarized using a descriptive statistical technique. The results were expressed as a

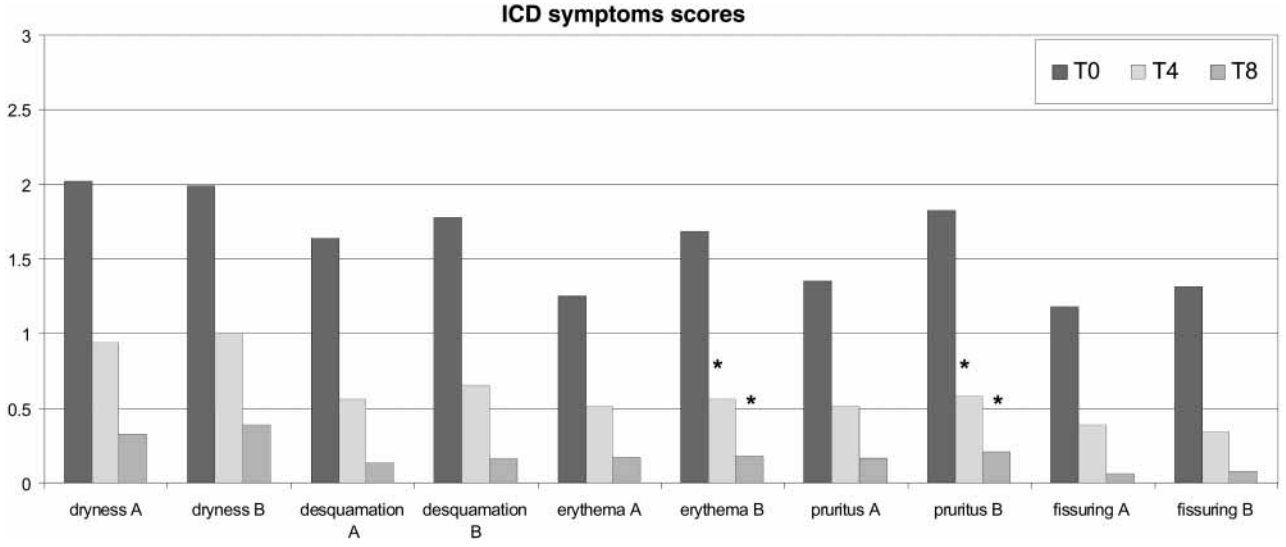

Fig. 1. *=$p<0.05$ in favour of group B versus group A. A=patients treated with skin lipid mixture alone; B=patients treated with skin lipid mixture+topical corticosteroids.

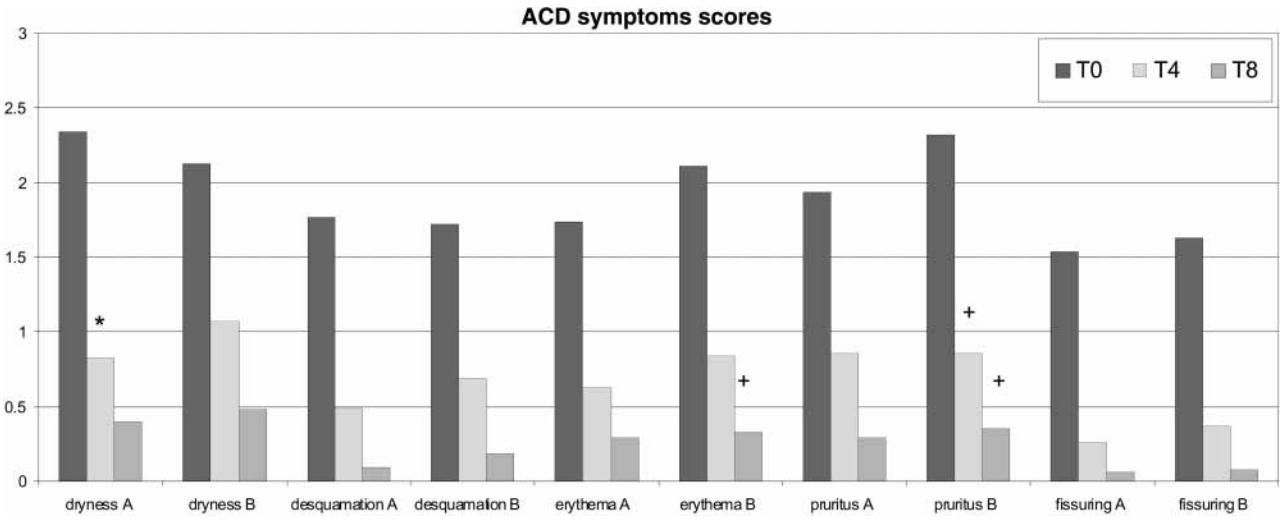

Fig. 2. *=$p<0.05$ in favour of group A versus group B; +=$p<0.05$ in favour of group B versus group A. A=patients treated with skin lipid mixture alone; B=patients treated with skin lipid mixture+topical corticosteroids.

mean±SD. The *2-way ANOVA test* was used for statistical evaluation at scheduled visits versus baseline in each group; for multiple comparison *t-Dunnet test* was used. Between the 2 treatment groups, the comparison of the median values on the differences observed at each scheduled visit versus baseline was performed using *t-test for independent data*. Non-parametric statistics were also used where appropriate. Statistical significance was defined as $p<0.05$.

Results

Irritant contact dermatitis

Both treatment groups (Table 2) had a statistically significant improvement in all parameters considered at week 4 and at week 8 versus baseline (Fig. 1, Fig. 4).

The mean values of the differences after 4 and 8 weeks versus baseline showed no statistically-significant difference between the 2 treatment groups for dryness ($p=0.281$ and $p=0.300$, respectively; ns), scaling ($p=0.589$ and $p=0.261$, respectively; ns) and fissuring ($p=0.097$ and $p=0.390$, respectively; ns), (Fig. 1).

A statistically-significant difference in favour of combined therapy was shown for erythema ($p<0.001$ and $p<0.001$, respectively), pruritus ($p<0.001$ and $p<0.001$, respectively) and overall severity disease ($p=0.008$ and $p=0.031$, respectively), (Fig. 1, Fig. 4).

Allergic contact dermatitis

Both treatment groups had a statistically significant improvement in all parameters considered at week 4 and at week 8 versus baseline (Fig. 2, Fig. 4). The mean values of the differences after 4 and 8 weeks versus baseline showed no statistically-significant difference between the 2 treatment groups for scaling ($p=0.086$ and $p=0.355$, respectively; ns), fissuring ($p=0.847$ and $p=0.726$, respectively; ns) and overall disease severity ($p=0.528$ and $p=0.600$, respectively; ns), (Fig. 2, Fig. 4).

A statistically-significant difference in favour of the skin lipid mixture was shown in dryness at week 4 ($p<0.001$; p=ns at week 8); in favour of combined therapy for erythema at week 8 only ($p=0.034$; p=ns at week 4) and for pruritus at week 4 and at week 8 (respectively $p=0.019$ and $p=0.041$) (Fig. 2).

Atopic dermatitis

Both treatment groups had a statistically-significant improvement in all parameters considered at week 4 and at week 8 versus baseline (Fig. 3, Fig. 4). The mean values of the differences after 4 and 8 weeks versus baseline showed no statistically-significant difference between the 2 treatment groups for dryness ($p=0.612$ and $p=0.613$, respectively; ns) and scaling ($p=0.125$ and $p=0.166$, respectively; ns) (Fig. 3).

A statistically-significant difference in favour of combined therapy was shown for erythema at week 4 ($p=0.041$; p=ns at week 8), pruritus at week 8 ($p=0.018$; p=ns at week 4), fissuring at week 4 and week 8 ($p=0.002$ and $p=0.031$), and overall severity disease at week 4 ($p=0.007$; p=ns at week 8) (Fig. 3, Fig. 4).

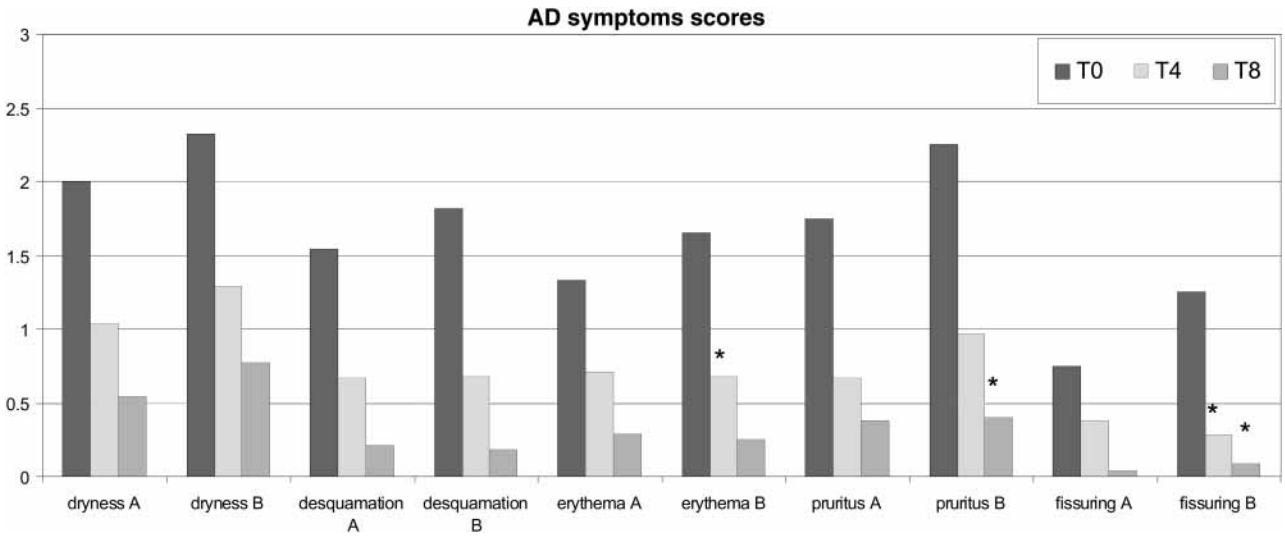

Fig. 3. *=$p<0.05$ in favour of group B versus group A. A=patients treated with skin lipid mixture alone; B=patients treated with skin lipid mixture+topical corticosteroids.

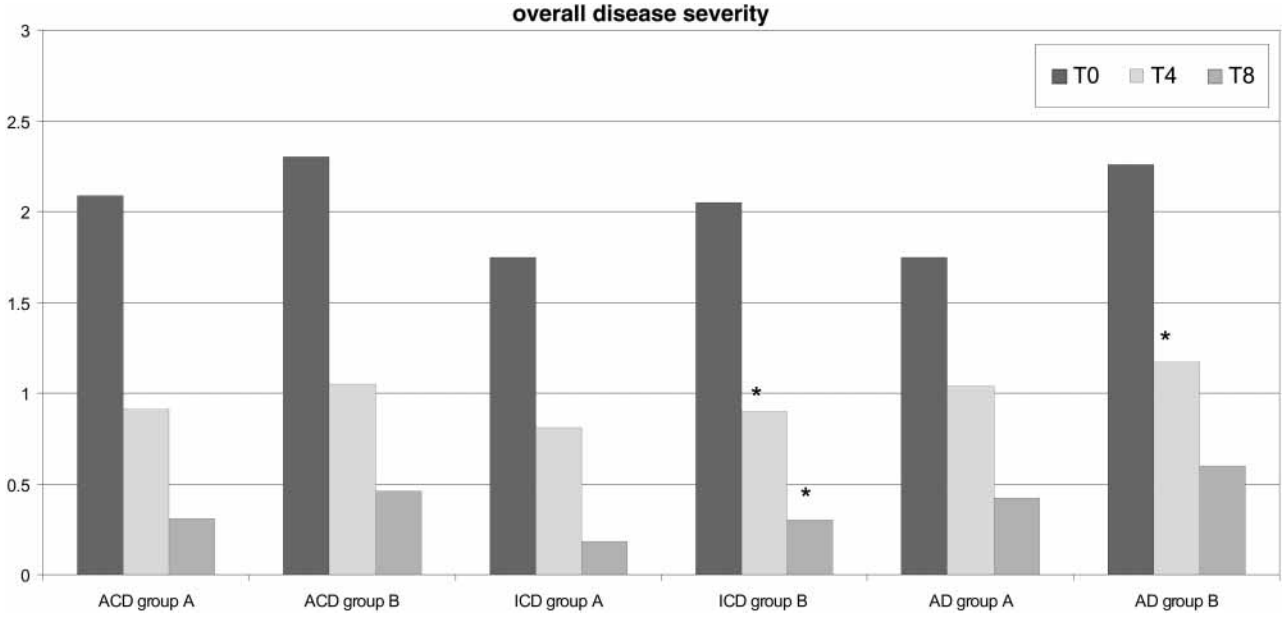

Fig. 4. *=$p<0.05$ in favour of group B versus group A. A=patients treated with skin lipid mixture alone; B=patients treated with skin lipid mixture+topical corticosteroids.

Discussion

Disturbance of skin barrier function occurs in a number of skin diseases, including atopic dermatitis (AD) and irritant/allergic contact dermatitis (ICD, ACD).

The skin barrier can be damaged in several ways, such as by frequent exposure to mechanical stress (construction workers, carpenters), lipid extraction by oils, grease or organic solvents, long-term exposure to water (cleaners, kitchen workers, fish or paper industry workers), detergents or liquid soap (housewives). As a consequence of TEWL increase, the skin becomes dry. Skin barrier disturbance triggers the production of cytokines which stimulate lipogenesis but can also increase inflammatory responses and induce the appearance of eczema. As a result of a damaged skin barrier, irritant and sensitizing substances can more easily penetrate the skin, increasing the risk of development of ICD/ACD. Topically, application of a lipid mixture has been shown to be useful in pro-

viding "ready to use" lipids to the SC in order to promote repair of a deranged barrier; however, the usefulness of this model has been mainly shown in animal models and few data in humans are available (13–16). Furthermore, these studies have been performed using standardized irritation models, but not in real clinical conditions, where many environmental and in-use cofactors can influence the outcome of therapy.

Our study shows how an optimized lipid mixture included in nanoparticles (17) can be helpful in promoting barrier repair and improving skin condition in different dermatoses characterized by barrier damage.

Both treatment groups improved significantly at weeks 4 and 8 both in AD and ICD/ACD. In particular, no significant differences between the treatments at weeks 4 and 8 were detected for dryness, scaling, fissuring (ICD/ACD only) and overall disease severity (ACD only) (i.e., the clinical parameters more related to SC efficiency) in all the pathologies investigated. The combined treatment (lipids+topical corticosteroids) leads to a more significant effect on erythema, presumably due to the corticosteroid's vasoactive characteristics, and on pruritus as a probable consequence of a suppressed release of inflammatory mediators. The overall disease severity was in favour of the combined treatment in ICD and AD. These findings support the view that optimized lipid mixtures can be helpful in improving barrier properties in clinical conditions, even though not exerting a pharmacological effect. Therefore, their use could be indicated as a support for barrier restructuring during the acute phases of ICD/ACD or AD in association with pharmacological therapy, or as a preventive maintenance measure to counteract barrier disruption and reduce risk factors before the onset of clinical signs of irritant contact dermatitis.

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