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REVIEW ARTICLE

Barrier Repair Therapy in Atopic Dermatitis: An Overview

Kam Lun Hon · Alexander K. C. Leung · Benjamin Barankin

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Abstract Atopic eczema or dermatitis (AD) is a chronically relapsing dermatitis associated with pruritus, sleep disturbance, psychosocial symptoms, and impaired quality of life. It affects 10–20 % of school-aged children, and there is evidence to suggest that this prevalence is increasing. Filaggrin (filament-aggregating protein) has an important function in epidermal differentiation and barrier function. Null mutations within the filaggrin gene cause ichthyosis vulgaris and appear to be a major risk factor for developing AD. The affected skin of atopic individuals is deficient in filaggrin degradation products or ceramides. Avoidance of triggering factors, optimal skin care, topical corticosteroids, and calcineurin inhibitors are the mainstays of therapy for AD. Proper moisturizer therapy can reduce the frequency and intensity of flares, as well as the need for topical corticosteroids or topical calcineurin inhibitors. Recent advances in the understanding of the pathophysiological process of AD involving filaggrin and ceramides has led to the concept of barrier therapy and the production of new moisturizers and topical skin products targeted to correct reduced amounts of ceramides and natural moisturizing factors in the skin with natural moisturizing factors, ceramides, and pseudoceramide products. Emollients, both creams and ointments, improve the barrier function of the stratum corneum by providing it with water and lipids. Studies on AD and barrier repair treatment show that adequate lipid replacement therapy reduces the inflammation and restores epidermal function. We reviewed 12 randomized trials and 11 cohort studies and found some evidence that certain products had therapeutic efficacy in improving clinical and/or biophysical parameters of patients with AD. Nevertheless, study methods were often flawed and sample sizes were small. Additional research is warranted to better understand the optimal formulary compositions. Also, long-term studies would be important to evaluate whether lipid barrier replacement therapy reduces bacterial colonization or prevents progression of the atopic march.

K. L. Hon (✉)
The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
e-mail: ehon@hotmail.com

A. K. C. Leung
The University of Calgary, Alberta Children's Hospital, Calgary, AB, Canada

B. Barankin
Toronto Dermatology Centre, Toronto, ON, Canada

1 Introduction

Atopic dermatitis (AD) is a chronically relapsing dermatitis associated with atopy (asthma and hay fever) [1]. The pathogenesis of AD involves complex interactions between susceptible genes, immunological factors, skin barrier defects, infections, and neuroendocrine and environmental factors [2, 3]. AD involves defective cell-mediated immunity related, in part, to an imbalance in two subsets of CD4 T cells that creates a predominance of T-memory cells in the T-helper 2 pathways and preferential apoptosis of interferon-γ-producing T-helper 1 memory and effector T cells. T-helper 2 cells express a set of cytokines that stimulate the proliferation and differentiation of B lymphocytes, upregulate the expression of adhesion molecules on endothelial cells, and contribute to the hypereosinophilia, high serum IgE levels, sustained cutaneous inflammation, histamine release, and pruritus characteristics of AD [2–7]. AD also involves many complex immune

pathways in addition to abnormal cell-mediated immunity [1]. Hence, it is often debated whether AD is primarily a skin disorder with systemic associations or a systemic atopic disease with skin manifestations in early childhood, which 'marches' to the airways in subsequent years. Regardless of the two fundamentally different viewpoints, barrier repair therapy remains a key management facet.

2 The Role of the Skin Barrier in Atopic Dermatitis Pathogenesis

Xerosis or dry skin results from reduced amount of ceramides in the skin, with enhanced transepidermal water loss [8, 9]. Xerosis predisposes to the development of microfissures and cracks in the epithelium, which favors the entry of allergens and microorganisms [10]. Abnormal proteins (filaggrin and related proteins) and lipid (ceramide) metabolism are responsible for the complex AD pathophysiology. It has been shown that loss-of-function mutations in the filaggrin (filament-aggregating protein) gene (*FLG*) predispose to AD [11–15]. Filaggrin is a key component of the epidermal differentiation complex of the stratum corneum in the epidermal layer of human skin. It forms the natural moisturizing factor (NMF) in the stratum corneum and plays an important role in the barrier function of the skin [16]. The keratohyalin granules in the granular layers are predominantly composed of profilaggrin [17]. Filaggrin aggregates the keratin cytoskeleton system to form a dense protein–lipid matrix that is cross-linked by transglutaminases to form a cornified cell envelope [16, 17]. The latter prevents epidermal water loss and impedes the entry of allergens, infectious agents, and chemicals [16]. It is believed that defective epidermal function is related to the down-regulation of the *FLG* gene [18–22]. Recent findings have shown that the affected skin of atopic individuals is deficient in filaggrin degradation products [23].

A reduced content of ceramides has also been noted in both normal and affected skin of patients with AD [23–25]. The reduction in ceramides may result from increased sphingomyelin deacylase activity and reduced production of ceramides by keratinocytes [5]. Ceramides serve as important water-holding molecules in the extracellular space in the horny layer [26]. A deficiency in ceramides results in enhanced transepidermal water loss, dry skin, and increased permeability to environmental irritants and allergens [5]. Increased transepidermal water loss is observed in patients with AD [27, 28]. In addition, keratinocyte-derived antimicrobial peptides known as cathelicidins and β defensins are deficient in the skin of patients with AD [27, 29]. These peptides help in the host defense against bacteria, viruses, and fungi. The skin barrier disruptions of AD associated with loss-of-function mutations in *FLG* are thought to provide a nidus for allergic sensitization to food and aeroallergens, which can then lead to increased allergic disease [30]. Thus, therapies aimed at restoration of the barrier function are thought to play a role, not only in the effective treatment of AD, but also in the prevention of further allergic disease development.

The role of lipids in the stratum corneum, primarily ceramides, fatty acids, and cholesterol, in relation to AD has been delineated [31]. Ceramides, cholesterol, and free fatty acids are the main lipid classes in the stratum corneum. Twelve ceramide subclasses in human stratum corneum have been identified, with a wide chain length distribution [32, 33]. Janssens et al. [34] performed a comprehensive analysis of ceramide composition and lipid organization in non-lesional stratum corneum of patients with AD and control subjects. The authors found that the level of ceramides with an extreme short chain length was drastically increased in the stratum corneum of AD patients, which lead to an aberrant lipid organization and a decreased skin barrier function. Changes in stratum corneum lipid properties correlated with disease severity but were independent of *FLG* mutations. They demonstrated that changes in ceramide chain length and lipid organization are directly correlated with the skin barrier defects of non-lesional skin of AD patients Ceramide-dominant, physiological, lipid-based barrier repair topical emulsions focus on physiologic lipid replacement therapy to restore the normal balance of the epidermal barrier. In comparison with other emollients such as petrolatum that form a more superficial occlusive barrier, ceramide-dominant moisturizers are thought to permeate the stratum corneum, be taken up by keratinocytes, processed in lamellar bodies, and re-secreted back into the stratum corneum to become a part of the dermal matrix [35–37].

Structural analysis of commercial ceramides can be performed by gas chromatography-mass spectrometry. In one study, 83 structures of trimethylsilylated ceramides were identified in 11 different commercial products [38]. Topical application of K6PC-9p (*N*-ethyl dihydrogenphosphate-2-hexyl-3-oxo-decanamide), a synthetic ceramide derivative of PC-9S (*N*-ethanol-2-mirystyl-3-oxo-staramide), exerts beneficial effects in an animal model of skin inflammation and AD [39]. Although not disclosed in publications, some of these commercial ceramides are described in their respective patents [40].

Repairing the skin barrier or preventing barrier dysfunction is now believed to be the cornerstone of management of AD. Successful treatment requires a holistic approach that consists of avoidance of triggering factors, optimal skin care, pharmacotherapy during acute exacerbations, and education of patients/caregivers [2, 41, 42]. Pharmacotherapy usually consists of topical application of

corticosteroids or calcineurin inhibitors, and less commonly systemic agents [2]. Of note, while topical corticosteroids have been the mainstay of therapy for more than 60 years, unlike calcineurin inhibitors, they will in fact impair the skin barrier function. Dry skin is more prone to itching and chapping and hence secondary infection and subsequent perpetuation of AD. Hydration of the skin increases drug penetration as hydration causes swelling of the stratum corneum, rendering it more permeable to drug molecules. The key to management of AD and dry skin conditions, especially in between episodes of flare-ups, is the frequent and proper use of an appropriate moisturizer, especially soon after the skin has absorbed water (e.g. after a shower or washing hands) [2, 13, 18, 43–45].

Moisturizers can be in the form of creams, emollients, lotions, or ointments [40, 46, 47]. Creams are semisolid emulsions (mixtures of oil and water). Creams are either water-miscible and readily washed off, or oily and not so easily washed off. They are divided into two types: oil-in-water creams, which are composed of small droplets of oil dispersed in a continuous phase; and water-in-oil creams, which are composed of small droplets of water dispersed in a continuous oily phase. Oil-in-water creams are more comfortable and cosmetically acceptable as they are less greasy and more easily washed off using water. Water-in-oil creams are more difficult to handle, but many drugs that are incorporated into creams are hydrophobic and will be released more readily from a water-in-oil cream than an oil-in-water cream. Water-in-oil creams are also more moisturizing as they provide an oily barrier, which reduces water loss from the stratum corneum. Barrier creams often contain water-repellent substances such as dimethicone or other silicones that protect against irritation or repeated hydration. They are the preferred forms of treatment for exudative dermatoses.

Emollients are fats or oils in a two-phase system (one liquid is dispersed in the form of small droplets throughout another liquid). Emollients soften the skin by forming an occlusive oil film on the stratum corneum, preventing drying by evaporation from the deeper layers of skin and rendering it more pliable in dry AD, ichthyosis, and psoriasis. Emollients minimize dryness and are the mainstay in treating mild AD.

Lotions are aqueous solutions or suspensions that cool diffusely inflamed unbroken skin by evaporation. They should be applied frequently. Lotions are also used to apply drugs to the skin when only a thin layer of the preparation is intended to be applied over a large surface area.

Ointments are semisolid substances that are greasy, normally anhydrous, and insoluble in water. The most commonly used ointment bases consist of soft paraffin or a combination of soft paraffin with liquid paraffin and hard paraffin. Due to their anhydrous nature, ointments do not require any preservatives. They have the advantages of being more moisturizing and more occlusive than creams, and form a protective film over the skin. Because of their marked occlusive effect, ointments are not suitable for acute weeping, crusting skin conditions, particularly in the intertriginous areas. Today, there are ointments that possess both hydrophilic and lipophilic properties so that they become water-soluble and can be washed off readily. Within the emollient (intercellular lipids) category, moisturizers contain a variable mix of ceramides, cholesterol, and free fatty acids [37].

The use of moisturizers helps the skin maintain a defensive barrier effect, which is defective in patients with AD [48]. Dry skin and skin hydration correlates with disease severity [28, 42]. The skin condition may improve significantly with the liberal use of moisturizers such that the use of topical corticosteroids or calcineurin inhibitors maybe minimized or avoided [40].

A number of topical moisturizers are available on the market. The actual ingredients and concentrations in most of these products are a commercial secret of individual pharmaceutical companies. However, the active ingredients are cited on the packaging. The type of moisturizer or emollient should be tailored to the individual skin condition as well as the child's needs and preferences [49–51].

3 Barrier Repair Therapy in Atopic Dermatitis Management: A Review of the Evidence

We searched MEDLINE, Embase, and the Cochrane Library for articles published using the following search terms in combinations: 'barrier', 'barrier repair', 'eczema', 'atopic', 'atopic dermatitis', 'natural moisturizing factor', 'ceramide', and 'pseudoceramide'. We selected literature from mainly the past 20 years but did not exclude commonly referenced and highly cited older articles. We included and described all randomized trials, case series, and bench studies in barrier repair therapy for AD, with limits activated (Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, English, published in the last 10 years). All editorials, letters, practice guidelines, reviews, and animal studies were excluded. In addition, the bibliographies of the retrieved articles and our own research database were also hand searched.

As of December 2012, 50 articles were retrieved from PubMed using the keywords 'barrier therapy' and ('atopic dermatitis' or 'eczema') and limits of 'clinical trial' and 'humans'. Using Clinical Queries under PubMed Tools, and Clinical Trials under More Resources, we retrieved 31, 13, and 18 references under Clinical Study Categories (narrow), Systematic Reviews, and Clinical Trials, respectively. All randomized controlled trials and relevant

case series and bench studies were included. Review articles that did not provide any information on barrier therapy for AD were excluded.

Between 2001 and 2012, there were 13 reported randomized trials (Table 1). Seven of these trials included pediatric patients. These trials generally suffered from a lack of sample size calculation and small sample size. A number of them only used clinical or biophysical parameters for evaluation of efficacy. Few evaluated quality-of-life issues and none evaluated patient acceptability of treatment. The treatment effects were generally small or non-existent. In cohort, case control, or case series between 1999 and 2012 (Table 2, $n = 12$), the sample sizes were generally small and suffered similar problems as the randomized trials. In these studies, the effects on the skin barrier of a number of compounds were evaluated, including corticosteroids, immunomodulating agents (such as pimecrolimus), hydrogel, pseudoceramides, or their precursors, and NMFs. Some of these studies are summarized as follows (also see Tables 1, 2).

Moisturizers containing urea, α-hydroxy acids, hyaluronic acids, or ceramides have been shown to improve the integrity of the stratum corneum [44, 52–55]. More recently, ceramides, pseudoceramides, and NMFs have been studied and added to commercial moisturizers to mimic natural skin moisturizing factors and lipids [56, 57].

Several studies aim to show that moisturizer therapy can reduce the frequency and severity of flares and reduce the need for topical corticosteroids or topical calcineurin inhibitors [58–61]. Ceramide-dominant emollients influence both transepidermal water loss and the expression of antimicrobial peptides in patients with AD [27]. The use of ceramide-dominant emollients is associated with restoration of the permeability barrier function with concomitant improvement of antimicrobial defense in patients with AD. Frankel et al. [58] evaluated the short-term effectiveness of a ceramide-hyaluronic acid emollient foam as compared with pimecrolimus cream 1 % in the treatment of AD within a wide age group of subjects with active AD at baseline. In this study, both pimecrolimus cream and the ceramide-hyaluronic acid emollient foam exhibited efficacy in patients with mild-to-moderate AD. The authors concluded that both the ceramide-hyaluronic acid emollient foam and the pimecrolimus cream 1 % work well in the treatment of AD in children and adults, with no associated adverse effects.

Chamlin et al. [44] assessed the efficacy of a ceramide-dominant, physiologic lipid-based emollient, when substituted for previously used moisturizers. All subjects continued prior therapy (e.g., topical tacrolimus or corticosteroids), only substituting the barrier repair emollient for their prior moisturizer. Follow-up evaluations showed SCORing Atopic Dermatitis (SCORAD) index values improved significantly in 22 of 24 patients by 3 weeks, with further improvement in all patients between 6 and 20 or 21 weeks. Transepidermal water losses, which were elevated over involved and uninvolved areas at entry, decreased in parallel with SCORAD scores and continued to decline even after SCORAD scores plateaued. Both stratum corneum integrity (cohesion) and hydration also improved slowly but significantly during therapy. The authors concluded that a ceramide-dominant barrier repair emollient represents a safe, useful adjunct to the treatment of childhood AD, and transepidermal water loss is at least as sensitive an indicator of fluctuations in AD disease activity as are SCORAD values. The study supports the outside-inside hypothesis as a component of pathogenesis in AD and other inflammatory dermatoses that are accompanied by a barrier dysfunction.

Park et al. [27] investigated the relationship between antimicrobial and barrier factors by measuring the changes in transepidermal water loss and antimicrobial peptides after topical application of tacrolimus and a ceramide-dominant emollient in patients with AD. A total of only three patients with AD were treated with tacrolimus on one lesion and ceramide-dominant emollient on another lesion for 4 weeks. The mean changes of transepidermal water loss and antimicrobial peptides showed no statistical difference between sites. The authors concluded that tacrolimus and a ceramide-dominant emollient influence both transepidermal water loss and antimicrobial peptide expression in patients with AD. It should be noted that the sample size in this study was quite small, and outcome measurements were focused.

Hon et al. [41] evaluated whether the amount of emollient and skin cleanser used correlates with AD severity, skin hydration, or transepidermal water loss, and whether liberal usage alters disease severity, skin hydration, and transepidermal water loss. Patients with AD had significantly higher transepidermal water loss and lower skin hydration in the studied sites than healthy controls. Although both skin dryness and skin hydration were improved, there was no significant improvement in SCORAD scores or transepidermal water loss after 2 weeks [41]. The outcome measures in this study included clinical scores, skin hydration, transepidermal water loss, and global assessment of treatment measurements. This open-label, cohort study with healthy controls showed essentially no significant efficacy despite some improvement in skin hydration.

In another study, Hon et al. [62] recruited 33 patients with AD to study the clinical and biophysiological effects of twice-daily application of a pseudoceramide-containing cream. The skin hydration significantly improved 1 month following the use of the pseudoceramide cream, but there was no change in transepidermal water loss, AD severity,

Table 1 Randomized trials of barrier therapy for atopic dermatitis

Population	Design: therapy	Outcome measures	Adverse effects	Validity	Remarks	References
Adults	ran, pg, db: glycerol, urea	Skin capacitance and TEWL	Nil sig	No sample size calculation, no clinical parameters	Limited evaluations of skin barrier; efficacy not well demonstrated; no sig difference	[74]
Adults	db, ran: tacrolimus or betamethasone valerate	Barrier function (rate of water accumulation)	Nil	No sample size calculation, no clinical parameters	Limited evaluations of barrier function only	[75]
Adults	ran, pc, db: glycerol	Clinical and biophysical	Nil	No sample size calculation, small	Some improvement in biophysical but not clinical parameters	[76]
Adults	ran, controlled: ceramide-containing liquid cleanser and moisturizing cream added to high-potency corticosteroid	Clinical only	Nil	No sample size calculation, no biophysical parameters, poorly described study	No evaluation of skin barrier function, ceramide enhanced treatment outcome of a high-potency corticosteroid	[69]
Adults	db, within-patient, vehicle-controlled: pimecrolimus cream 1 %	Clinical and biophysical	Nil	No sample size calculation, small sample size	Clinical and biophysical efficacy demonstrated	[77]
Not specified	ran: pimecrolimus vs. betamethasone	Clinical, stratum corneum hydration, TEWL, dye penetration, electron microscopic evaluation of barrier structure	Betamethasone led to epidermal thinning	No sample size calculation, small sample, no placebo	Efficacy demonstrated; both drugs normalized epidermal differentiation and reduced epidermal hyperproliferation; betamethasone was superior in reducing clinical symptoms and epidermal proliferation	[78]
Not specified	5-center, investigator-blinded, ran: EpiCeram® [a] vs. fluticasone	Clinical only	Nil	No sample size calculation, small sample, no placebo	Biophysical improvement not demonstrated	[71]
Adults	ran, controlled, pg, pro, mc: urea-containing moisturizer	Clinical + time to relapse, biophysical	Nil	No sample size calculation, complicated 2-phase randomization	Efficacy demonstrated, but two randomization processes involved	[79]
Adults	db, ran, pc: topical gluco-oligosaccharide and collagen tripeptide F	Clinical and biophysical	Nil	No sample size calculation, small sample size	Efficacy demonstrated	[80]
Pediatric	ran, investigator-blinded: Atopiclair™ [b] vs. EpiCeram® [a] vs. Aquaphor Healing Ointment® [c]	Clinical only	Nil sig	Three arms, no placebo, small sample size, no sample size calculation	No efficacy difference demonstrated	[54]
Adults	db, split-body: HLA-based foam vs. ceramide-containing emulsion cream	Clinical only	Nil sig	No placebo, very small sample size, no sample size calculation	Clinical efficacy of HLA foam over ceramide cream	[66]

Table 1 continued

Population	Design: therapy	Outcome measures	Adverse effects	Validity	Remarks	References
Adults and pediatric	Open-label, investigator-blinded, side-by-side, controlled: fluocinolone vs. vehicle	Clinical, QOL, and biophysical parameters	Nil	Very small sample size, no sample size calculation	Efficacy of a super-potent corticosteroid demonstrated	[81]
Not specified	Single-center, investigator-blinded, ran, split-body: hydrogel vs. moisturizing lotion control	Only biophysical	Nil	No placebo, very small sample size, no sample size calculation	Only biophysical parameters	[82]

[a] EpiCeram® is a ceramide-dominant emulsion with a 3:1:1 ratio of ceramides, cholesterol, and free fatty acids (PuraCap Pharmaceutical LLC, South Plainfield, NJ, USA)

[b] Atopiclair™ is a glycyrrhetinic acid-containing barrier repair cream (Invida Holdings Pte Ltd, Singapore)

[c] Aquaphor Healing Ointment® is a petroleum-based skin protectant moisturizer (Beiersdorf, Hamburg, Germany)

db double-blind, *HLA* hyaluronic acid, *pc* placebo-controlled, *mc* multicenter, *pg* parallel-group, *pro* prospective, *QOL* quality of life, *ran* randomized, *sig* significant, *TEWL* transepidermal water loss

or quality of life in these patients. The pseudoceramide cream improved the skin hydration but not the severity or quality of life over a 4-week usage. This study similarly demonstrated no significant clinical efficacy. The effect of a pseudoceramide-containing physiologic lipid mixture as a vehicle for a mid-potency topical corticosteroid was evaluated in an oxazolone-induced AD-like murine model [63]. The topical corticosteroid in physiologic lipid mixture showed a significantly decreased infiltrate of inflammatory cells and a reduced number of adherent *Staphylococcus aureus* compared with the results of the topical corticosteroid in a polyethylene glycol/ethanol vehicle. The authors concluded that the pseudoceramide-containing physiologic lipid mixture as a vehicle for a topical corticosteroid enhanced the anti-inflammatory effect of the topical corticosteroid and accelerated restoration of the skin barrier. This study is different from the study by Lee et al. [63] in that those investigators combined a corticosteroid and a pseudoceramide. The investigators only evaluated inflammatory cell infiltration, not clinical efficacy.

A multi-lamellar emulsion (MLE) is a pseudoceramide-containing physiological lipid mixture that can restore and improve the barrier function of skin [64]. Co-application of MLE and 1.0 % hydrocortisone showed less impairment in the epidermal permeability barrier function, skin hydration, and skin surface pH than hydrobase. Stratum corneum integrity, evaluated by measuring transepidermal water loss after repeated tape stripping, showed less damage with MLE co-application. Long-term application of topical hydrocortisone induced skin atrophy, measured by a reduction in skinfold and epidermal thickness, and in the number of epidermal proliferating cell nucleus antigen (PCNA)-positive keratinocytes. Co-application of MLE did not affect the skinfold or epidermal thickness, but the number of PCNA-positive keratinocytes was reduced to a lesser degree with MLE use. The investigators suggested that co-application of MLE is effective in reducing the local adverse effects of low-potency topical corticosteroids and supports the therapeutic efficacy of physiological lipid mixtures on skin barrier function [65]. These investigators evaluated the interaction between an MLE and a topical corticosteroid. Clinical efficacy, such as disease severity and quality of life parameters, were not studied.

Not all investigators revealed efficacy with ceramide-containing products. Draelos [66] evaluated a newly developed hyaluronic acid-based, pH neutral foam technology formulated to maximize humectancy and normalize transepidermal waster loss for its ability to optimize barrier function while minimizing unnecessary irritation. Subjects applied the hyaluronic acid-based emollient foam to one side of the body and the reference ceramide-containing emulsion cream to the opposite side. Both formulations

Table 2 Cohort studies and case series of barrier therapy for atopic dermatitis

Population	Design: therapy	Outcome	Adverse effects	Remarks	References
Adults and adolescents	20 pts: topical evening primrose oil	Stabilizing effect on the stratum corneum barrier with the water-in-oil emulsion not the amphiphilic emulsion	Nil	A small series, no clinical effects demonstrated	[83]
Pediatric	24 children: TriCeram® [a]	Clinical and biophysical parameters improved	Nil	Small series, demonstrating improvement in both clinical and biophysical parameters	[44]
Pediatric	113 children: EpiCeram® [b]	Clinical only	Nil	No evaluation of biophysical parameters, limited scientific data for this review	[70]
Adults	Markov simulation model	Cost effectiveness only	Nil	Demonstrated cost effectiveness but not clinical efficacy	[84]
Adults	3 pts: tacrolimus vs. ceramide-dominant emollient	Biophysical only	Nil	Biophysical not clinical parameters, limited scope	[27]
Pediatric	67 pts, case control AD vs. non-AD pts: emollient use	Clinical, QOL and biophysical parameters	Nil	Controlled study for 4 weeks only, emollient alone does not alter AD severity, QOL or TEWL	[41]
Pediatric	33 pts, prospective observational study: pseudoceramide-containing cream	Clinical, QOL and biophysical parameters	Nil	A small series, emollient alone does not alter AD severity, QOL or TEWL	[62]
Adults	19 healthy volunteers: betamethasone vs. tacrolimus vs. emollient	Biophysical parameters only	Nil	A small series, clinical parameters not studied, betamethasone and tacrolimus improved biophysical parameters	[68]
Adult and pediatric	Bilateral comparison: pimecrolimus cream 1 % vs. medical device ceramide-HLA emollient foam	Limited clinical parameters	Nil	Limited efficacy demonstrated	[58]
Mice	Physiological lipid mixture with pseudoceramide (myristyl/palmityl oxostearamide/arachiamide MEA: PC-9S)	Biophysical parameters only	Nil	Reduced barrier damage due to topical glucocorticosteroid usage	[65]
Infants	Compliance study, 10 infants: EpiCeram® [b]	Biophysical parameters	Nil	Not a clinical study	[72]
Pediatric	24 pts: Restoraderm® [c]	Clinical parameters of age, objective SCORAD score, pruritus score, sleep disturbance score, skin hydration, TEWL, topical corticosteroid use, oral antihistamine use, acceptability	Nil	Clinical and biophysical improvement are associated with pt acceptability of the product	[85]

[a] TriCeram® is a ceramide-dominant, lipid-based emollient with ceramides 2.1 %, free fatty acids 0.8 %, and cholesterol 0.8 %. Exact nature of ceramides not mentioned. This product is no longer available in the USA

[b] EpiCeram® is a ceramide-dominant emulsion with a 3:1:1 ratio of ceramides, cholesterol, and free fatty acids (PuraCap Pharmaceutical LLC, South Plainfield, NJ, USA)

[c] Cetaphil Restoraderm® is an emollient with ceramide precursor lipids and moisturizing factors (Galderma Laboratories LP, Fort Worth, TX, USA)

AD atopic dermatitis, *HLA* hyaluronic acid, *pt(s)* patient(s), *QOL* quality of life, *SCORAD* SCORing Atopic Dermatitis Index, *TEWL* transepidermal water loss

achieved statistically significant improvement in all clinical signs and symptoms of AD by week 4; however, the hyaluronic acid-based foam achieved statistically significant improvement in overall AD severity by week 2, whereas the ceramide-containing emulsion cream did not. The subject's preference statistically significantly favored the foam in terms of ability to spread, ability to moisturize, ease of use, and lack of odor. In addition, the foam was preferred for effectiveness and ability to soothe. The investigators concluded that the prescription hyaluronic acid-based foam device offers an aesthetic formulation with excellent efficacy in patients requiring an environment for barrier repair with mild to moderate AD. This randomized trial is different from many other trials in that it took patient preferences into consideration and demonstrated efficacy.

While many products make extensive claims of skin rejuvenation, many of the beneficial effects of these products are actually due to the moisturizers they contain (ingredients like glycerol, petrolatum, and dimethicone). Some approved, newer, prescription-device moisturizers on the basis of reducing transepidermal water loss are significantly more expensive than traditional moisturizers, and recent literature does not indicate that they are more effective than their over-the-counter counterparts [67]. In a randomized, controlled trial, Miller et al. compared an over-the-counter petroleum-based skin protectant moisturizer with prescription barrier creams (a glycyrrhetinic acid-containing barrier repair cream and a ceramide-dominant barrier repair cream) as monotherapy for children with mild-to-moderate AD and found the petroleum-based moisturizer clinically as effective, and more cost effective than, the prescription creams [54].

Few studies have compared barrier repair therapy with emollients, topical corticosteroids, and calcineurin inhibitors. One study of 19 healthy volunteers examined the effects of a topically applied corticosteroid, tacrolimus, and an emollient on stratum corneum lipids and barrier parameters [68]. After 1 week, each area was challenged with a 24-h sodium lauryl sulphate patch test. The ceramide/cholesterol ratio was increased in betamethasone- and tacrolimus-treated skin compared with emollient-treated skin. No differences in ceramide subgroups were found between treatment regimens. Pretreatment with betamethasone or with tacrolimus caused a decreased inflammatory response to sodium lauryl sulphate compared with emollient. The investigators concluded that treatment with betamethasone and tacrolimus had a positive effect on the ceramide/cholesterol ratio and susceptibility to irritant reaction compared with an emollient. This study is limited by the short study period of only 1 week.

Recent studies have shown that EpiCeram® (a specific combination of ceramides, cholesterol, and fatty acids [in the ratio of 3:1:1] that mimics those naturally found in the skin; PuraCap Pharmaceutical LLC, South Plainfield, NJ, USA) has efficacy similar to that of a mid-potency topical corticosteroid and has a favorable safety profile [69, 70]. However, these studies were of limited usefulness in that they did not report objective measurements to demonstrate efficacy of treatment.

Among all the randomized trials listed in Table 1, there was only one multicenter (five centers), investigator-blinded, randomized trial with very small sample size, which demonstrated some clinical efficacy. Biophysical parameters were not measured in the trial [71]. Among all the cohort studies and case series listed in Table 2, there was only one relatively large pediatric series of 113 patients using EpiCeram® that demonstrated limited clinical data on efficacy but did not evaluate biophysical parameters [70].

AD is a complex disease. To date, these randomized trials and case series have provided inadequate evidence that barrier therapy alone may cure the disease. Physicians should help patients to establish realistic therapeutic goals and to choose the most acceptable moisturizer in combination with topical, systemic, and behavioral management.

4 Barrier Therapy: Recent Advances and Future Developments

Defects in skin barrier function are associated with an increased risk of AD and atopic sensitisation. A recent study investigated whether early usage of barrier therapy in neonates could prevent atopic sensitization. The investigators assessed the safety and compliance with daily application of a ceramide-dominant triple lipid formula (EpiCeram®), commencing in the neonatal period for the prevention of AD [72]. Ten infants with a family history of allergic disease were recruited into an open-label, phase I trial of daily application of EpiCeram® for 6 weeks. There were no adverse skin reactions to the study cream. The investigators concluded that the preliminary results support the safety and parental compliance with daily application of a ceramide-dominant formula for the prevention of AD. This small study provided the necessary ground work for a randomized clinical trial to evaluate EpiCeram® for the prevention of AD.

Research has also focused on dermal delivery systems that can best deliver an active substance through the stratum corneum, and the production of pseudoceramides, which possess properties necessary to improve the water barrier function of the stratum corneum [40]. Dermal delivery systems are compositions that typically contain skin permeation enhancers that may induce structural transformations of the bilamellar structure in the liquid crystalline

interdomain regions, and thus promote transdermal delivery of pharmacological substances. Conventional delivery systems that are thought to protect the skin from harmful substances are barrier ointments. The purpose of barrier ointments is to provide a film, and thereby create a layer, which is impermeable to environmental substances. Due to their impermeability, these ointments increase the body temperature of the treated area, as well as prevent perspiration, and thus render an uncomfortable sensation. The aforementioned dermal delivery systems are not formulated to deliver a substance to, or through, the human skin without permanently disrupting the stratum corneum's natural barrier function. Dermal delivery systems should ideally deliver treatment medication while preserving the natural barrier function of the stratum corneum.

5 Conclusion

Barrier repair therapy aims to target the pathophysiology of AD. A new concept in skin care is the incorporation of NMFs, ceramides, and pseudoceramide products into therapeutic moisturizers. Current research on efficacy of their use appears conflicting and inconsistent. Some studies showed only mild improvement of severity or skin hydration, while others demonstrated moderate corticosteroid-sparing effects. Many trials had very small sample sizes and did not evaluate all relevant clinical and biophysical parameters. Well designed, large-scale, randomized, placebo-controlled trials to document the therapeutic effects on disease severity, dermatologic biophysical parameters, quality of life, and patient acceptability are needed. The ideal skin barrier therapeutic agent is yet to be invented. Realistically, AD is a complex disease, and effective management should be individualized and holistic, and encompass an assessment of severity and impact on quality of life, treatment of the inflamed epidermal skin barrier, recognition and treatment of infection, and assessment and management of environmental and allergic triggers [73]. Patient and family education that seeks to maximize understanding and compliance with treatment is also important in all children with AD.

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