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CLINICAL INVESTIGATION ABOUT A COADJUVANT TOPICAL TREATMENT CONTAINING GLYCEROPHOSPHOINOSITOL AND PERILLA EXTRACT ON MILD TO MODERATE ATOPIC DERMATITIS

ESPERIENZA CLINICA DI UN TRATTAMENTO TOPICO COADIUVANTE A BASE DI GLICEROFOSFOINOSITOLO ED ESTRATTO DI PERILLA NELLA DERMATITE ATOPICA LIEVE E MODERATA

V. DI LERNIA, S. DONELLI, M. CORNA, O. NEMELKA, G. FILOSA, C. OCCELLA

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Clinical investigation about a coadjuvant topical treatment containing glycerophosphoinositol and perilla extract on mild to moderate atopic dermatitis

Esperienza clinica di un trattamento topico coadiuvante a base di glicerofosfoinositolo ed estratto di perilla nella dermatite atopica lieve e moderata

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***Aim*. In the involved epidermis of patients with atopic dermatitis (AD), changes in the metabolism of eicosanoids with increased quantities of the arachidonic acid-derived lipoxygenase products have been observed. Arachidonic acid serves as a substrate for cyclooxygenase and lipoxygenase enzymes whose products, prostaglandin E2 and leukotrien B4 are present in lesional skin of atopic subjects in biologically active concentrations. Glycerophosphoinositol (GPI) salts are semisyntetic derivatives of GPI, a natural cell component produced by lipid metabolism. Since GPI is able to negatively modulate the cytosolic phospholipase A2 (cPLA2) and thus to limit the cascade of event related to the arachidonic acid metabolism, there is rationale for its application in the management of skin inflammation associated to AD.**

***Methods.* The authors report their experience in a group of 30 subjects affected by mild to moderate AD who were treated for 4 weeks with a new topical compound containing GPI and perilla extract.**

***Results and conclusion.* All 30 patients completed the study with good results in the majority of cases. After 4 weeks, mean EASI score showed a decrease by 73%. Visuo-Analogue Scale (VAS) pruritus scale showed a decrease by 59%. GPI may represent a possible beneficial option in patients affected by mild to moderate AD, although this was a preliminary open, non randomized study based on a short-term observation.**

KEY WORDS: Perilla - Administration, topical - Dermatitis, atopic.

Obiettivo. Nell'epidermide affetta da dermatite atopica sono presenti alterazioni del metabolismo degli eicosanoidi con quantità aumentate di prodotti derivati dall'acido arachidonico. Quest'ultimo agisce come substrato per enzimi quali cicloossigenasi e lipoossigenasi i cui prodotti, la prostaglandina E2 e il leukotriene B4, rappresentano potenti mediatori infiammatori presenti in concentrazioni elevate nella cute affetta da dermatite atopica. I sali di glicerofosfoinositolo (GPI) sono derivati semisintetici del glicerofosfoinositolo, un componente cellulare prodotto dal metabolismo dei lipidi, in grado di modulare negativamente la fosfolipasi A2, l'enzima coinvolto nella mobilizzazione dell'acido arachidonico, limitando di conseguenza la cascata di eventi correlati al metabolismo dello stesso acido. Grazie alle sue proprietà il GPI si presenta come un composto innovativo con un razionale interessante per l'utilizzo nella dermatite atopica.

Metodi. Gli autori riportano la propria esperienza in un gruppo di soggetti affetti da dermatite lieve o moderata trattati per 4 settimane con un topico contenente GPI ed estratto di perilla. Tutti i 30 soggetti completavano lo studio mostrando una riduzione media del 73% dell'EASI rispetto al basale e del 59% dei valori di prurito registrati con la scala Scala Visuo-Analogica (VAS).

Risultati e conclusioni. Sulla base di questo studio il GPI rappresenta un composto con possibile azione benefica nella dermatite atopica di grado lieve o moderato, sebbene i dati conclusivi vadano considerati tenendo conto dei limiti degli studi aperti non randomizzati e di breve termine.

PAROLE CHIAVE: Perilla - Trattamento topico - Dermatite atopica.

Atopic dermatitis (AD) is one of the most frequent chronic inflammatory skin diseases, with a prevalence of about 18% to 25% in children [1] and an increasing incidence worldwide, particularly in industrial countries.[2]

The skin in AD may exhibit significant abnormalities in barrier function, consisting of increased transepidermal water loss, decreased stratum corneum moisture content, increased permeability to hydrophilic substances, decreased lipids/ceramides, decreased barrier to infectious agents, decreased endogenous humectants, likely increased epicutaneous antigen absorption. Disruption of the skin barrier, either resulting from an intrinsic genetic defect in epidermal skin barrier formation or as a result of an environmental alteration, is able to lead to sensitization and atopic diseases. The type of the immune responses evolves with time, starting with elevated skin levels of Th17 associated cytokines (IL-6, IL-17A and IL-23) and involving

TABLE I.—*Patients' characteristics and study outcome.*

Patient	EASI T0	EASI T2	Pruritus T0	Pruritus T2	Rescue medication	Spreadability	Skin absorption
1	4	1	5.5	4.5	Yes	E	G
2	3.2	1.7	2.5	1.5	No	VE	O
3	1.6	1.2	2.5	2	Yes	E	O
4	4.6	4	4.5	4	No	E	O
5	7.2	7	7	7	No	E	G
6	5	1	8.5	3	Yes	E	G
7	6.2	2.7	4	2	Yes	VE	G
8	2.2	0.6	5	2	No	VE	G
9	12.4	7.6	7	3.5	Yes	E	G
10	2.6	0.6	4	2	No	E	G
11	10.5	0	3	0.5	No	VE	G
12	2.6	0	2	0	No	VE	G
13	6.7	0	2	0.5	No	VE	G
14	5.2	0	3	0.5	No	E	G
15	8.4	3.6	5	3	No	VE	G
16	3	1	3	3	No	E	G
17	7.8	0	3	0.5	No	VE	G
18	7.5	0	4	0.5	No	VE	G
19	7.8	0.9	4	1	No	E	G
20	4.5	0.9	3	0.5	No	VE	G
21	4.8	0.5	4	1	No	E	G
22	8.4	1.4	8.5	0.5	No	E	G
23	0.6	0	2.5	0	No	E	G
24	1	0	2.5	0	No	E	G
25	5.6	3.2	7	5.5	No	RE	G
26	2.5	0	3.5	0.5	No	E	G
27	2.1	0	0.5	0	No	E	G
28	10.2	1.2	7	0.5	No	E	G
29	1.2	0.4	1.5	0	No	VE	G
30	0.8	0	2	0.5	No	VE	G
Mean	5.006666667	1.35	4.05	1.666666667			

Spreadibility: VE: very easy; E: easy; RE: rather easy; D: difficult. Skin absorption: G: good; O: optimal; I: insufficient

later Th2 cytokines (IL-4 and IL-13), whereas IFNγ levels remain unchanged.[3] Skin barrier removal by tape stripping has been recently shown to polarize skin dendritic cells to promote a Th2 response upon allergen exposure.[4]

In the involved epidermis of patients with AD, changes in the metabolism of eicosanoids with increased quantities of the arachidonic acid-derived lipoxygenase products have been observed. Free arachidonic acid concentrations in epidermis are significantly elevated, suggesting an abnormality in transformation of phospholipids to other lipid classes. Arachidonic acid serves as a substrate for cyclooxygenase and lipoxygenase enzymes whose products, prostaglandin E2 and leukotriene B4 are potent biological inflammatory mediators. Both products are present in lesional skin of atopic subjects in biologically active concentrations.[5] For these reasons, a compound able to limit the cascade of events related to the arachidonic metabolism could be helpful in the management of atopic dermatitis.

The aim of our study was to evaluate the effect of a topical product, containing glycerophosphoinositol (GPI) as a coadjuvant treatment of mild to moderate AD.

Materials and methods

This study was a 4-week, prospective, open-label, multicenter, outpatient study conducted in 30 subjects with mild to moderate AD, age range 4-16 years. The product used was a topical ointment containing glycerophosphoinositol and perilla extract (trade name: Osmintop ointment; manufacturer: Valetudo, Italy). The topical compound was applied twice daily over a time period of 4 weeks.

Eligibility requirements included investigator assessed diagnosis of AD on the basis of Hanifin and Raijka criterias and degree of mild–moderate severity defined by Investigator's Global Assessment (IGA). Exclusion criteria were defined as severe manifestations of atopic eczema, other inflammatory, infectious skin or systemic diseases, severe accompanying diseases. Accompanying medications of any kind (systemic or topical) were not permitted during the study period and for 2 weeks prior to study enrollment. Rescue medication with a topical corticosteroid (desonide 0.5% cream) twice daily for one week was allowed in case of worsening of the eczema after medical supervision.

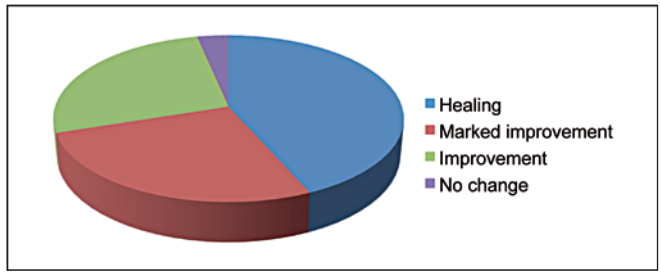

Figure 1.—Percentage of patients considered "healed", "greatly improved", "improved" and "no clinical changes" after 4 weeks of treatment with GPI

The following parameters were assessed at baseline (time 0), week 2 (time 1), and week 4 (time 2): IGA scored on a scale of 4-point scale (0: almost absent, 4: very severe); Eczema Area and Severity Index (EASI) for each body area affected by AD (head and neck, upper limbs, torso, and lower limbs). Erythema, infiltration, excoriations and lichenification were assessed at each site and scored on a scale from 0 (absent) to 4 (severe). EASI scores were tallied to obtain a single composite score, which ranged from 0 (no disease anywhere on the body) to 72 (severest disease on all body areas). The patients' personal assessment of the intensity of pruritus was determined using the Visual Analogic Scale (VAS) for pruritus (0=absent; 10=severe). At week 4, parents of participants completed a personal assessment of spreadability on a scale from 0 (very easy) to 4 (difficult) and skin absorption of the compound on a scale from 0 (optimal) to 4 (insufficient).

Primary outcome parameters were the changes of IGA, EASI score, VAS pruritus scale after 4 weeks of treatment, compared with the initial examination. At every visit adverse events were asked for and documented.

Results

All of the 30 patients enrolled completed the study. Patients' characteristics and study outcomes are summarized in Table I. Whole body EASI decreased significantly from baseline. Mean EASI score was 5 at time 0 and 1,35 at time 2 (week 4) showing a mean decrease of 73%. VAS pruritus

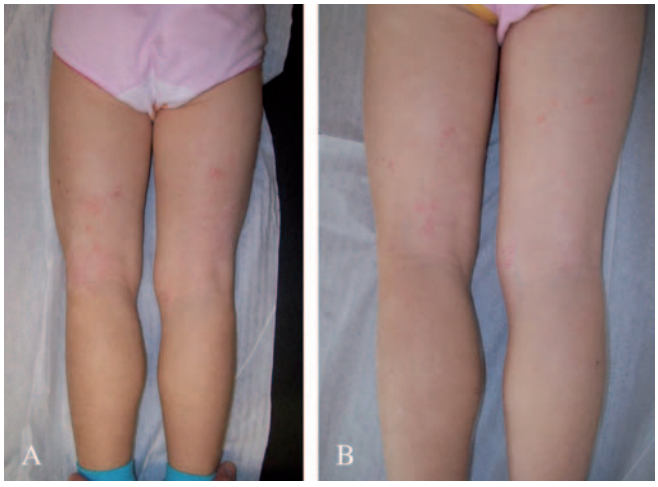

Figure 2.—A) Patient 9 at baseline, EASI score 12.4; B) after 4 weeks, EASI score 7.6.

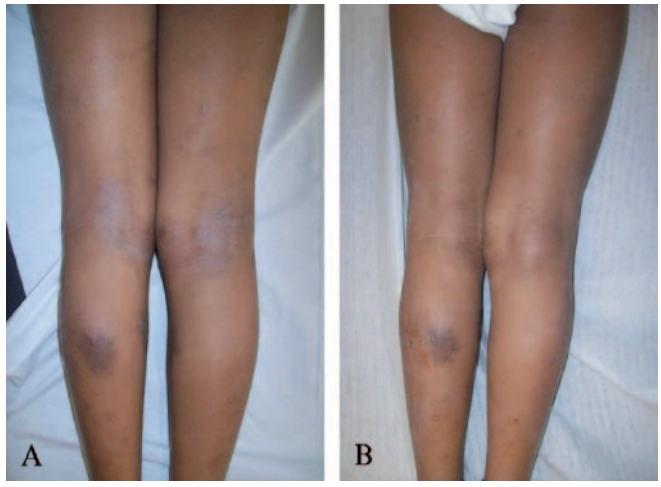

Figure 3.—A) Patient 7 at baseline, EASI score 6.2; B) after 4 weeks, EASI score 2.7

scale showed a similar efficacy trend falling from a mean score of 4.05/10 at time 0 to a mean score of 1.66/10 at time 0 with a percentage decrease by 59%. After the 4 weeks of treatment, on the basis of changes in IGA, investigators considered 13 patients as "healed", 8 patients as "greatly improved", 8 patients as "improved", 1 patient with no clinical changes (Figure 1). Five out of 30 patients required to utilize the "rescue medication" with desonide cream for a week. Figure 2 A, B and Figure 3 A, B show two examples of patients considered as "improved". Parents of participants were generally pleased with the cosmetic attributes of the compound. Spreadability was rated usually as very easy or easy and skin absorption as optimal or good. No significant adverse events were reported. Six patients reported a short-term stinging sensation after the application. However in all these six cases the duration of burning was only a few minutes, consequently the treatment had always been completed.

Discussion

Eicosanoids, products derived from arachidonic acid metabolism, include prostaglandins and leukotrienes and are implicated in the pathogenesis of several inflammatory diseases, including AD.[6] In particular prostaglandin E2 and leukotriene B4 are potent inflammatory mediators originating from membrane-derived arachidonic acid through the 5-lipoxygenase pathway. In AD a topical application of lipoxygenase products causes psoriasis-like lesions, suggesting their inflammatory roles in the pathogenesis.[7] In mammals the mobilization of arachidonic acid is greatly due to the activation of cytosolic phospholipase A2 (cPLA2).

GPI salts are semisyntetic derivatives of GPI, a natural cell component produced by lipid metabolism. GPI is able to negatively modulate the cPLA2 and thus to limit the cascade of event related to the arachidonic acid metabolism.[8]

Hence GPI salts present an interesting rationale for their use in the management of skin inflammation associated to AD. In the compound evaluated in this study, GPI presents as choline salts. Choline is a precursor of the synthesis of phosphatildylcholine and sphingomyelin. Since ceramides are central intermediates of sphingolipid metabolism,[9] a potential role not only in skin inflammation, but also in skin barrier restoring can be claimed for this compound.

Topical corticosteroids, which have anti-inflammatory and antipruritic properties, are considered the first-line therapy for the management of AD and in particular of disease exacerbations. However the complexity of this skin disease, has made it especially difficult to find effective treatments and prevention strategies. Adverse effects of topical corticosteroids, which include atrophy, striae, tel-

angiectasia, and dryness, are correlated with their potency. A possible systemic side effect of repeated use of topical steroids is reversible suppression of the hypothalamic-pituitary-adrenal axis. Because drug penetration is greater and more rapid in infants who have thinner strata cornea and increased surface area to body mass ratios, the potential for adverse effects is greatest in younger patients, the same group most likely to have AD. Thus, once disease activity is controlled, corticosteroids should be applied intermittently, if long-term therapy is needed to control intermittent flares. The least potent preparation that adequately controls the disease process should be selected.

Topical steroids can further reduce the skin barrier function, which is considered the main pathogenetic event of AD.[11] Immunomodulatory agents include topical tacrolimus and pimecrolimus. In 2005 the FDA issued "black box" warnings for pimecrolimus cream and tacrolimus ointment because of potential safety risks, including skin cancers and lymphomas. However, these concerns are not supported by current data.[12] In particular, a corticosteroid, triamcinolone, is able to cause more depletion in UV-irradiated CD1a(+) epidermis than pimecrolimus.[12] Both tacrolimus and pimecrolimus are not approved for children younger than 2 years.

Treatment of AD must focus on restoring the skin barrier and reducing flares. Theoretically GPI seem to target these objectives. Our results in a cohort of 30 patients followed-up prospectively for a short-term observation showed that a compound containing GPI may represent a possible therapeutic option for mild to moderate AD. Indeed EASI score and VAS for itching showed a significant decrease after 4 weeks of treatment.

Conclusions

The conclusions of this study have the limitations being those of open label, non-randomized studies and short-term observations. Further observations in daily practice are necessary to confirm our preliminary observations.

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