Use of a Palmitoylethanolamide-Containing Nonsteroidal Cream for Treating Atopic Dermatitis: Impact on the Duration of Response and Time Between Flares

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A patented nonsteroidal cream containing palmitoylethanolamide (PEA), an endogenous fatty acid deficient in patients with atopic dermatitis, has been approved by the US Food and Drug Administration for treatment of atopic dermatitis in both the adult and pediatric populations. The formulation also contains lipids, including hydrogenated lecithin, palm glycerides, and Olea europaea, designed to decrease transepidermal water loss through simulation of the intercellular lamellar structure of the epidermal barrier. This article reports results from an investigator-blinded, split-body, randomized trial completed in both adults and children with symmetric atopic dermatitis. The study was designed to evaluate the impact of the PEA-containing nonsteroidal cream on duration of response and time between flares. At onset of disease flare, patients were treated on 1 side of the body with the study cream in combination with a designated midpotency topical corticosteroid (clocortolone pivalate 0.1% cream) twice daily and on the other side with a designated moisturizer cream in combination with the same designated topical corticosteroid twice daily for up to 4 weeks. The time to clearance on each side was documented. Once disease clearance was achieved, patients discontinued the topical corticosteroid and continued using the study cream and moisturizer cream on their previously designated application sides. Time to next flare on each side was documented. Patient assessments of response and product preference were also recorded, as were adverse events. Patients were monitored over a study period of up to 20 weeks.

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PEA Function

PEA is an endogenous fatty acid known to interact with cannabinoid 2 receptors on mast cells and believed to modulate immune response to triggers, primarily through mast cell stabilization and downregulation of the Th_2 lymphocyte cytokine response seen in association with atopic disease (Figure 1).[1] The use of a cream containing not only PEA but also lipids designed to facilitate epidermal barrier repair has been shown to reduce transepidermal water loss, increase PEA levels in treated skin, and exhibit anti-inflammatory activity.[1-3] In one experimental model, PEA was shown to downregulate the expression of interleukin 4, a finding that appears to be significant, since interleukin 4 production is upregulated in atopic dermatitis.[4] The PEA-containing nonsteroidal cream has been evaluated in more than 3000 patients, with demonstrated efficacy in reducing the signs and symptoms of eczematous dermatitis.[3]

How Is the PEA-Containing Nonsteroidal Cream to Be Positioned in the Management of Atopic Dermatitis?

This formulation may be used in both adults and children and is not restricted in anatomic region of application or duration of use. Its predominant roles appear to be: (1) adjunctive therapy used in combination with topical corticosteroids or topical calcineurin inhibitors at the onset of an eczematous flare and (2) maintenance therapy applied to flare-prone areas (ie, antecubital region, popliteal region, and face)

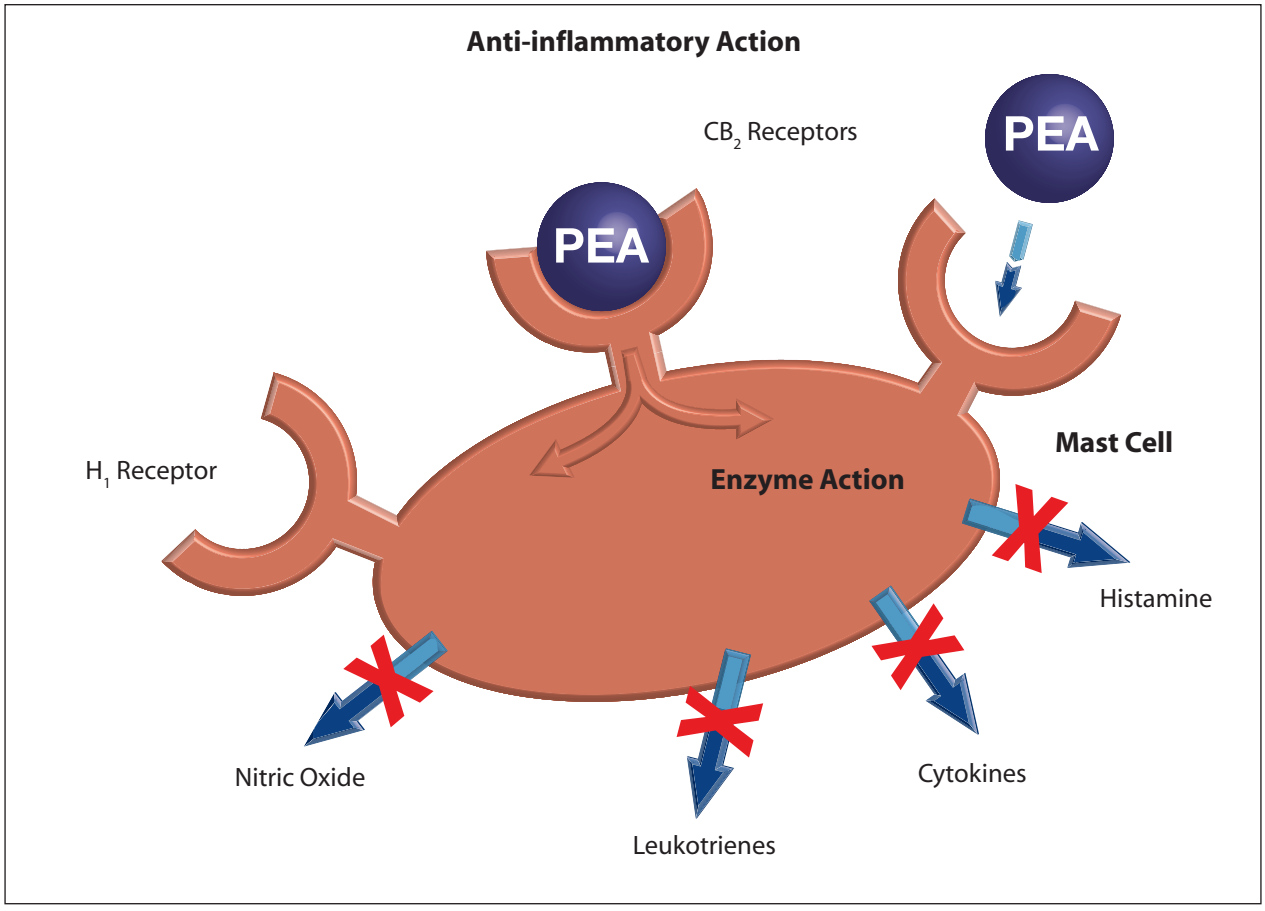

Figure 1. Palmitoylethanolamide (PEA) binding to cannabinoid 2 (CB_2) receptors on mast cells. H_1 indicates histamine H_1.

between exacerbations of atopic dermatitis to extend the duration of response and decrease the need for other therapies (Figure 2).[5]

Patient Demographics

This was an investigator-blinded, split-body, randomized trial of children and adults with atopic dermatitis. There were 43 patients enrolled in the study (25 children, 18 adults).

The ages of the children ranged from 4 to 15 years (mean age, 8 years). Fourteen were male and 11 were female. Sixteen of the children were white, 4 were Asian, 3 were Hispanic, and 2 were African American. All enrolled children completed the trial.

The adults ranged in age from 19 to 41 years (mean age, 27 years). Ten were male and 8 were female. Eight were white, 4 were Asian, 3 were Hispanic, and 3 were African American. Fifteen adults enrolled in the trial completed it; the remaining 3 did not complete the trial because work or travel obligations did not permit them to follow up on schedule.

Patients were included if they presented with a flare of atopic dermatitis of moderate severity and symmetric involvement of the upper or lower extremities with involvement of the antecubital or popliteal regions (target sites for evaluation). The antecubital region was the target area in 19 of the children and 11 of the adults; the popliteal region was the target area in 6 of the children and 7 of the adults.

Patients were excluded if they had used a prescription topical corticosteroid or topical calcineurin inhibitor within 1 week of study entry. Patients treated with systemic antihistamines up until the time of study entry were included provided the agents were discontinued before study initiation and not used throughout the entire study period. Also excluded were patients undergoing immunosuppressive therapy, such as with systemic corticosteroids, cyclosporin, azathioprine, or systemic tacrolimus, and those treated with phototherapy, including the use of commercial tanning beds.

Patients presenting with any condition determined by the investigator as possibly interfering with study results

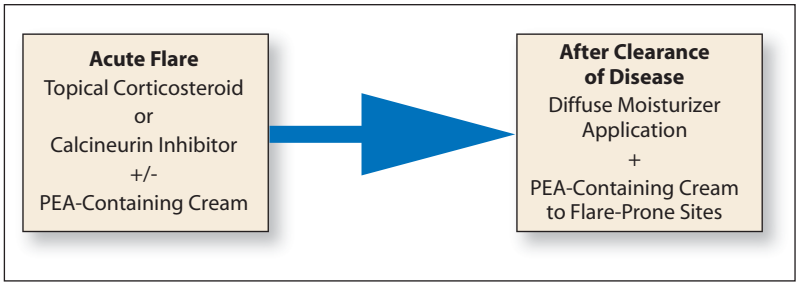

Figure 2. Stages of use of palmitoylethanolamide (PEA)–containing nonsteroidal cream in atopic dermatitis.

were excluded. Pregnancy determined prior to enrollment or documented during the study was also an exclusion criterion. A urine pregnancy test was performed on all female patients older than 16 years prior to enrollment and at the end of the study.

Study Design

Patients were treated at onset of disease flare on 1 side with the PEA-containing nonsteroidal cream in combination with the designated midpotency topical corticosteroid twice daily and on the other side with a designated moisturizer cream in combination with the same designated topical corticosteroid twice daily for up to 6 weeks.

All patients were supplied with the same brand of gentle skin cleanser and were instructed on proper use. The designated products were applied to all affected regions. The time to clearance on each side was documented based on follow-up at weeks 2 and 4.

After complete disease clearance was achieved, patients discontinued topical corticosteroid use and continued use of the PEA-containing nonsteroidal cream and moisturizer cream to their previously designated application sides twice daily with the target sites identified and also continued use of the gentle skin cleanser. Time to next flare on each side was documented based on patient diaries and follow-up visits every 2 to 4 weeks. Flare was defined as the reappearance of pruritus, visible eruption ("rash"), or both at the target site (designated antecubital or popliteal region). Patients or caretakers (where applicable) were instructed to indicate in the diary any development of pruritus ("itching") with or without erythema ("redness"), eruption ("rash"), or both at the target sites.

Five patients (4 children and 1 adult) were monitored over a study period of 20 weeks, and 35 patients were followed for 12 weeks after topical corticosteroid discontinuation. As a result, time-to-flare results were based on a 12-week follow-up period for consistency of reporting.

Patient assessment of response, product preference, and adverse events was also recorded.

Study Results

Figure 3 compares the complete clearance rate of the initial disease flare at weeks 2 and 4 for both sides of the body treated with either the topical corticosteroid in combination with the PEA-containing nonsteroidal cream or the topical corticosteroid in combination with the designated moisturizer cream. All patients in both groups were completely clear by week 6.

In the second phase of the study, after complete clearance was achieved and topical corticosteroid therapy was discontinued, the mean time to flare for the side treated with the PEA-containing nonsteroidal cream alone was 79.2 days for children and 72.4 days for adults. For the side treated with the designated moisturizer cream alone, the mean time to flare was 50.3 days for children and 44.2 days for adults. The mean time to flare was prolonged on the sides treated with the PEA-containing nonsteroidal cream by 28.9 and 28.2 days in children and adults, respectively, as compared with the sides treated with the designated moisturizer cream.

There were no protocol violations warranting early patient discontinuation during the trial.

Patient Preference in Study Products

In comparing preference for either the PEA-containing nonsteroidal cream or the designated moisturizer cream used in the time-to-flare study phase, product preference was based on response to the question, "Which product would you prefer to use on an ongoing basis?" If the patient was younger than 10 years, the parent was queried to give the response.

Of the 40 patients who responded to the patient-preference survey, 29 (73%) chose the PEA-containing nonsteroidal cream and 11 (27%) chose the designated moisturizer cream.

Adverse Events

No patients discontinued the study because of adverse events. Mild, transient stinging was reported on 4 occasions by the parents of 2 of the children (ages 6 and 9 years) using the PEA-containing nonsteroidal cream. No serious adverse events were reported.

Comment

In adult and pediatric patients presenting with a flare of atopic dermatitis, overall results of this study indicated that the sides treated twice daily with a midpotency topical corticosteroid in combination with a

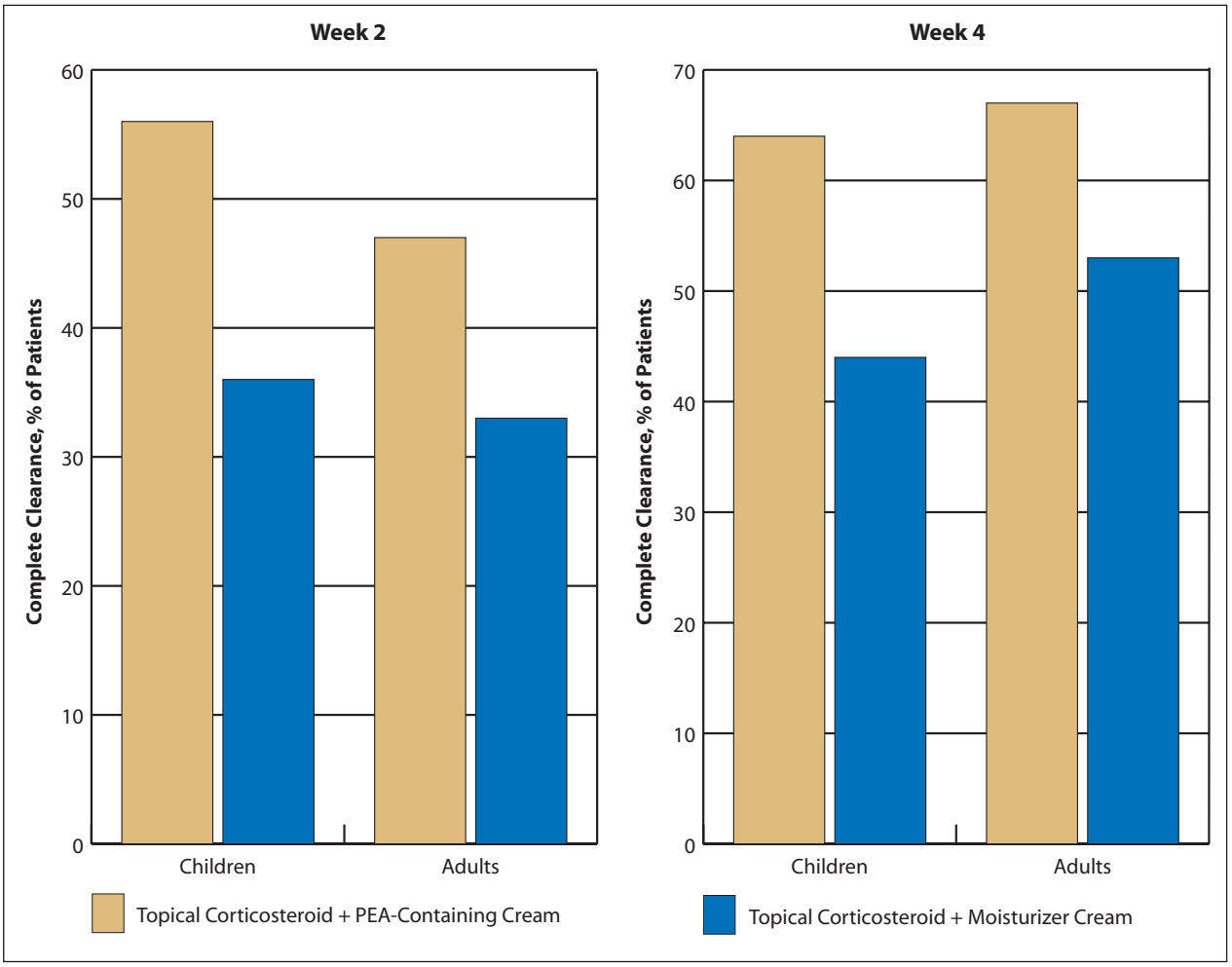

Figure 3. Initial clearance of disease flare at weeks 2 and 4 for patients with atopic dermatitis treated with a topical corticosteroid in combination with a palmitoylethanolamide (PEA)–containing nonsteroidal cream and patients treated with the same topical corticosteroid in combination with a moisturizer cream.

PEA-containing nonsteroidal cream demonstrated more rapid clearance than the sides treated twice daily with a topical corticosteroid in combination with a designated moisturizer cream.

During the maintenance phase after discontinuation of topical corticosteroid therapy, the mean time to flare was prolonged on the sides treated with the PEA-containing nonsteroidal cream by 28.9 and 28.2 days in children and adults, respectively, as compared with the sides treated with the designated moisturizer cream.

References

1. Facci L, Dal Toso R, Romanello S, et al. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. *Proc Natl Acad Sci USA*. 1995;92:3376-3380.
2. Zerweck C, Fraser J, Grove G. Efficacy of S236 cream in promoting barrier repair of razor-induced skin trauma. Poster presented at: 64th Annual Meeting of the American Academy of Dermatology; March 3-7, 2006; San Francisco, Calif.
3. Data on file. August C. Coral Gables, Fla: Stiefel Laboratories, Inc; 2006.
4. Berdyshev EV, Boichot E, Germain N, et al. Influence of fatty acid ethanolamides and delta9-tetrahydrocannabinol on cytokine and arachindonate release by mononuclear cells. *Eur J Pharmacol*. 1997;330:231-240.
5. Eberlein-Koenig B, Eicke C, Reinhardt HW, et al. Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA). Poster presented at: 64th Annual Meeting of the American Academy of Dermatology; March 3-7, 2006; San Francisco, Calif.