NEW NATURAL PPAR-α AGONIST FOR CHILDHOOD ATOPIC DERMATITIS: DERMOCORTICOID-SPARING AND QUALITY OF LIFE IMPROVEMENT

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Introduction

Atopic dermatitis (AD) is an inflammatory skin pathology associated with skin barrier disruption. The alteration of the skin barrier function is due to major lipid metabolism dysfunctions. Total amount of skin lipids is lowered which provokes a degradation of inter-cellular cement and a loss of cohesion of corneocytes. Moreover, ceramides and the ratio ceramides/cholesterol are significantly lowered. Finally, the extrusion of cellular lipids into the inter-cellular area is altered.
PPAR (Peroxysome-Proliferative-Activated Receptors) are transcription factors that regulate, upon ligand-dependent activation, the expression of target genes involved in many cellular functions (proliferation, differentiation, inflammatory response,..).
Three different PPAR have been identified: PPAR-α, -γ and β/δ. In the skin, PPAR-α is able to:

- inhibit inflammation in a mouse model of irritant or allergic contact dermatitis
- stimulate keratinocyte differentiation, while inhibiting proliferation
- enhance lipids metabolism,

thus PPAR-α seems to play a key role in the regulation of epidermal homeostasis. An emollient, specially formulated for AD, has been studied. It contains a patented Sunflower Oleodistillate (2%), obtained by molecular distillation, which is enriched 10 times in its unsaponifiable fraction compare to the edible oil. We have previously shown that Sunflower Oleodistillate® :

- is able to induce the synthesis of key epidermal lipids (e.g. ceramides x 3, cholesterol x 2) in human skin explants.
- is an activator of PPAR-α in CV1 cells
- is able to reduce TPA-induced inflammation (oedema and cytokines mRNA production)

In this work we sought to determine the effect of this new natural PPAR agonist in the management of AD and its potential contribution in the sparing of dermo-corticoides (DC).

Protocole

35 pediatricians who included 86 children with light to moderate atopic dermatitis have conducted a multicentric, randomized, blinded study. Children, aged from 4 months to 4 years (mean age 16 months) have been randomly assigned to 5 homogeneous groups, with 5 different treatments during 21 days (Table I).

Table I

Option	A	B	C	D	E
Morning	S	S+EM	S	S+EM	EM and S 1day / 2
Evening	S	S+EM	-	EM	EM

S = Desonide 0.05 % **EM : Emollient cream**

Clinical examinations, quality of life evaluations and auto-questionnaires were performed at D0, D7 and D21.

The items for clinical examination were those necessary to calculate the SCORAD index: Surface of atopic lesions, erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness of non-lesional skin, pruritus, loss of sleep.

There were 21 items for Quality of Life: IDQOL (The Infant's Dermatitis Quality of Life Index), DFI (The Dermatitis Family Impact Questionnaire) and degree of the eczema (http://www.ukdermatology.co.uk/quality/index.asp).

References:

1. Lawson V, Lewis-Jones MS, Finlay AY, Reid P, Owens RG. Br J Dermatol, 1998; 138: 107-113.
2. Lewis-Jones M S, Finlay A Y, Dykes P J. Br J Dermatol 2001 144: 104-10

Auto-evaluation questionnaires included questions about the efficacy of the emollient, its cosmetic characteristics and the degree of satisfaction of the user.

Statistical analysis
Kruskal and Wallis non parametric test for the comparison of the 5 treatments (A, B, C, D, E). Mann and Whitney non parametric test for the comparison of the two groups A-C and B-D-E. Non parametric test of Wilcoxon for paired samples for comparison between D7/D0 or D21/D0.

Results

Clinical examination

At D0, the SCORAD indexes were comparable [from 33.28 to 35.91, non statistically significant : p=0.92; Kruskal and Wallis]. **All five treatments induced a statistically significant (p<0.001; Wilcoxon) decrease of the SCORAD index at D7 and D21 (Figure 1). Moreover, at D21, the groups who applied the emollient (B/D/E) exhibit a more pronounced improvement of the SCORAD index compare to the groups with steroids alone (A/B).**

Figure 1

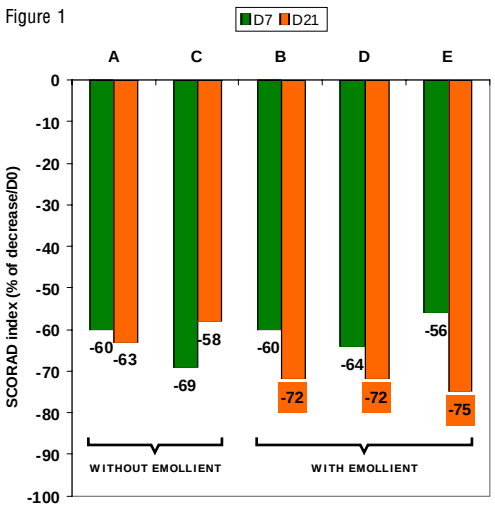

Figure 1: Evolution of the SCORAD indexes after 2 and 3 weeks of treatment without (A/C) and with emollient (B/D/E)

The global comparison of the 5 groups at D7 and D21 revealed no significant differences (p=0.715 and 0.813; Kruskal and Wallis) of SCORAD evolution between groups, confirming the effectiveness of the five treatments. This similarity of results allowed further comparisons two by two:

Comparison A/D and C/E: analysis of the 50% steroid sparing effect.
When doses of steroids are divided by two and replaced by applications of the emollient for 3 weeks, we observe no alteration of the treatment efficacy, but on the contrary, a most powerful effect on SCORAD: -74% (1X/D steroid + emollient) versus -63% (2X/D steroid) and -75% (1X/2D steroid + emollient) versus -63% (1X/D steroid).
This means that emollient has proven a 50% steroid sparing effect.

Comparison A/E: analysis of the 75% steroid sparing effect.
When we compare 2 applications/day of steroids and one application every other day + emollients everyday, we observe again that the power of the treatment is not reduced and even potentiate by the emollient effect of the emollient : -63% SCORAD without the emollient and -75% with the emollient.
Thus, the application of the emollient in alternate with topical steroids enables a 75% steroid sparing effect.

Table II .

	D7-D0		D21-D0	
	A	E	A	E
Surface of atopic lesions	-55%	-55%	-76%	-80%
Erythema	-69%	-44%	-59%	-62%
Edema/papules	-88%	-50%	-88%	-78%
Oozing/crust	-91%	-65%	-82%	-83%
Excoriation	-50%	-53%	-73%	-90%
Lichenification	-50%	-71%	-13%	-89%
Dryness of non lesional skin	-45%	-41%	-39%	-59%
Pruritus	-64%	-57%	-68%	-74%
Loss of sleep	-60%	-76%	-67%	-78%
SCORAD	-60%	-56%	-63%	-75%

TABLE II shows the evolution of each clinical item at D7 and 21 for groups A and E. It shows that the most rapid impact of the emollient (D7/D0) concerns the excoriations, the lichenification and the loss of sleep. This can be attributed to the soothing effect of the emollient. After 3 weeks (D21/D0) all items, except edema, are more improved in the group with the emollient (orange characters). This may be due to the restructuration of the cutaneous barrier function.

The statistical comparison of the evolution between A and E at D21 showed a significant difference for excoriation (p*<0.1) and at D7 and D21 for lichenification (p<0.01) in favor of the emollient, which means that it has a specific impact on these SCORAD parameters (Fig 2).**

Figure 2

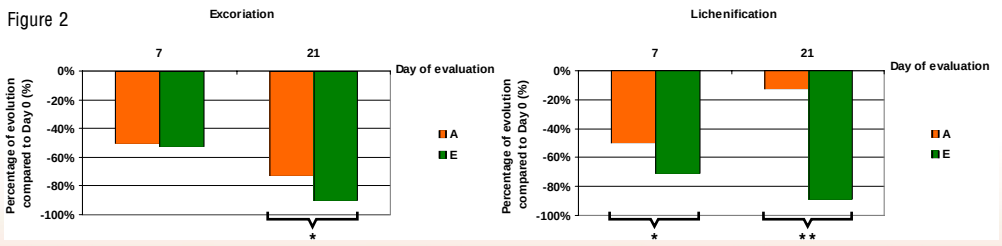

TABLE III illustrates the comparison between the two groups without emollient (A, C) and the three groups with emollients (B, D, E). This does not concern the amount of steroids but only the impact of adding emollients to the treatment of atopic dermatitis flares.
At D7, the therapeutic effects are mostly due to steroids. Here again, **the impact of the emollient is maximal at D21 with significant improvement of the SCORAD: -75% versus -64% (orange characters).**

Table III

	D7-D0		D21-D0	
	A-C	B-D-E	A-C	B-D-E
Surface of atopic lesions	-52%	-43%	-69%	-69%
Erythema	-61%	-54%	-58%	-61%
Edema/papules	-89%	-56%	-85%	-82%
Oozing/crust	-95%	-68%	-79%	-85%
Excoriation	-78%	-64%	-79%	-87%
Lichenification	-53%	-73%	-39%	-84%
Dryness of non lesional skin	-47%	-51%	-42%	-60%
Pruritus	-70%	-64%	-73%	-75%
Loss of sleep	-64%	-77%	-74%	-84%
SCORAD	-64%	-59%	-64%	-75%

Quality of life

The items exploring the quality of life of the patients (IDQOL) and their families (DFIQ) have been additioned to form a global score.

The following histogram (Figure 3) illustrates the data of the 5 treatment groups at D0 and D21. It shows that quality of life is mostly improved when emollient is applied: +75%, +70% and +73% for B, D, E Vs +57% and +46% for A, C. This means a 73% improvement of quality of life with the emollient + steroids compare to a 52% with the steroids alone.

Figure 3

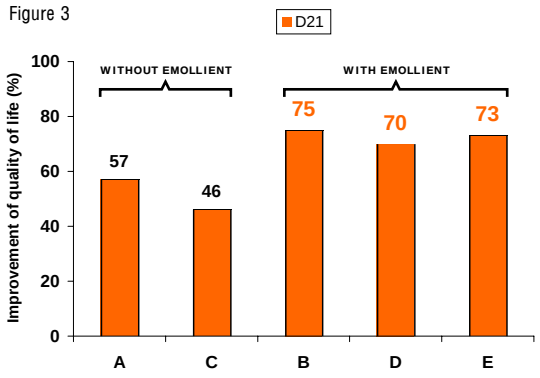

Figure 3 : Improvement of the Quality of life
(combination of the results obtained for the 21 items)

Significant differences between those two groups, in favor of the emollient, have been observed for 6 criteria at D21:
-Degree of the child eczema,
-Consequences on other familial activities,
-Consequences on domestic work,
-Consequences on sleep of other members of the family,
-Consequences on the shopping time for the whole family,
-Emotional stress of the parents.
Thus, the emollient justifies its complementary role in the treatment of AD flares with very significant improvement of Quality of Life of the child and his family.

Auto-evaluation questionnaires

(Only for groups B, D, E using the emollient)

TABLE IV summarizes the results of all the questionnaires: efficacy, cosmetic qualities, and pleasure of using the product. **This reveals very good performances for the emollient both on atopic plaques and on normally looking skin.**

Table IV

	B-D-E (% of good opinions)
Efficiency of the emollient applied on non lesional skin	96
Efficiency of the emollient applied on lesional skin	95
Cosmetic qualities of the emollient	85
On non lesional skin	73
On lesional skin	82

Conclusion

A new emollient containing PPAR-α agonist has been formulated for atopic dermatitis. In this study it has proven that :

- It is adapted even during atopic flares
- It has a major complementary therapeutic role with a **75% steroid sparing effect**
- It is a simple and mandatory way for improving quality of life of the atopic children and their parents.

Thus, this new emollient containing Sunflower Oleodistillate® (PPAR-α agonist) is a suitable strategy not only to improve skin conditions in AD patients, but also to reduce the consumption of steroid and to improve the quality of life of the children and their families.

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