

Comedolysis by a lipohydroxyacid formulation in acne-prone subjects

European Journal of Dermatology. Volume 13, Numéro 1, 65-8, January - February 2003, Thérapie

Summary

Auteur(s) : Emmanuelle UHODA, Claudine PIERARD-FRANCHIMONT, Gérald E. PIERARD, Department of Dermatopathology, University Medical Center, CHU du Sart Tilman Liège, Belgium.

Illustrations

ARTICLE

Acne is a multifactorial disease which begins to be visible when some pilosebaceous ducts become plugged with keratinocytes ultimately forming comedones. The ductal hypercornification can result from hyperproliferation of ductal keratinocytes or reduced separation of ductal corneocytes. Cells of the acne ductal hypercornification have more desmosomes and tonofilaments than is normal [1]. Instead of sloughing off in the normal fashion, ductal corneocytes remain cohesive. They eventually occlude the follicular infundibulum with a cornified plug. Sebum is also abundant and entrapped in this enlarged follicular reservoir [2].

Sun exposure may interfere in the global pathogenesis of acne. Sebum production is often increased [3, 4], *Propionibacterium acnes* suffers from partial photodynamic destruction [5], and the process of desquamation is altered [6, 7]. In addition, ultraviolet light induces other diverse biological effects in the distal portion of exposed pilo-sebaceous follicles. Indeed, cytokines are released from comedones [4] and some neuromediators including melanocortins are also likely to be involved [8, 9]. Under such circumstances, some acne-prone individuals develop kerosis corresponding to horny plugs collected in the follicular acro-infundibulum. These concurrent effects are probably involved in acne aestivalis [10], and are

possibly an initial step in the autumnal exacerbation of comedonal acne and acne vulgaris.

2-hydroxy-5-octanoyl benzoic acid is also known as beta-lipohydroxyacid (LHA). This compound is primarily a potent "keratolytic" agent, cleaving the corneodesmosomes to release the excess of corneocytes in hyperkeratotic conditions [11-13]. It also exhibits boosting effects on keratinocytes and dermal dendrocytes somewhat mimicking those of all-trans-retinoic acid [12, 14-18]. The lipophilic properties of LHA allow maximum concentration inside the stratum corneum, particularly in the sebum-enriched infundibulum of pilosebaceous units. Thus, the compound is likely to be trapped in lesional sebaceous follicles which represent a critical therapeutic target in comedonal acne. The product has shown efficacy in preventing and treating mild acne [19].

Comedogenicity and comedolysis can be studied in animal models and in humans [20]. One of the novel and most rewarding methods relevant for acne assessment relies on image analysis of video images recorded under ultraviolet light illumination [21].

The aim of the present study was to assess non-invasively the capacity of a proprietary LHA formulation to clear the horny plugs accumulated in the acro-infundibulum during the summertime on the face of acne-prone patients.

Materials and method

The protocol was approved by the local Ethics Committee. The comparative trial was performed in accordance with the Helsinki declaration and its subsequent revisions. The sample size was calculated to detect a difference in microcomedo density at the 5 % two-tailed significance with 80 % power. As we wanted to objectivate any comedolytic effect interfering with the natural history of acne over a short period of time, controls consisted of untreated skin rather than placebo-treated skin.

A total of 28 untreated, acne-prone Caucasian women with photosensitive skin were enrolled in the study. They were aged 24 ± 3 years. They experienced for several years exacerbations of acne at the end of summertime. They were otherwise healthy. Upon return from sunny holidays, one group of 14 randomized volunteers received the LHA formulation (Efficlark®, Roche Posay) to be applied twice daily on the face for 2 weeks. At that time of the year, the weather was cloudy in the Liège region. The other group of 14 volunteers remained untreated.

Due to the short study duration, the effect of treatment on inflammatory acne lesions was not considered. By contrast, tolerance was assessed by inquiring about stinging sensations and looking for erythema and desquamation.

A video camera equipped with an internal ultraviolet illumination source (Visioscan®, C + K Electronic, Cologne, Germany) recorded the pattern of the skin surface aspect according to a previously described method [21-23]. Images were recorded from the mid forehead at inclusion and twice weekly during the 14-day treatment phase. Kerosis was recognized as white tips located at the orifices of the pilosebaceous follicles. Pictures were recorded using a Sony video graphic printer UP-890CE ®. They were also digitalized in a 512 x 400 pixel frame. Image analysis of the area covered by kerosis was performed after a stepwise contrasting procedure followed by the holefill procedure

The number, mean area and total area of the keratotic follicular plugs were recorded in each subject. Means and SD were calculated in both groups of volunteers. Variance analysis was performed in each group to compare data obtained in time. A p value lower than 0.05 was considered significant.

Results

At inclusion, cornified follicular plugs were clearly identified on the forehead in 12/14 volunteers enrolled in the LHA group and in 10/14 volunteers enrolled in the untreated group (*Fig. 1*). Only these volunteers were considered for further evaluations. During the treatment period, the tolerance of the LHA formulation was excellent as no side-effect was reported or observed. Image analysis showed striking changes in the density of the follicular keratotic plugs. A remarkable comedolytic effect was evident in 10/12 LHA-treated patients (*Fig. 2*). A similar decline in the keratotic plug density was seen in only 3/10 untreated patients. In the LHA-treated group, the density in keratotic follicular plugs decreased sharply during the 14-day treatment reaching significance ($p < 0.001$) from day 7 on (*Fig. 3*). The mean area of the keratotic follicular plugs was little influenced by the treatment (*Fig. 4*). The total area of these structures decreased significantly from day 7 ($p < 0.05$), and furthermore at days 10 and 14 ($p < 0.001$) (*Fig. 5*). In the control untreated group, no significant changes in any of the evaluated morphometric parameters were yielded during the observation period.

Discussion

Many causes are probably involved in the pathogenesis of acne. Androgens, hyperactivity of the sebaceous gland, bacteria, genetics, drugs, occupation, and stressful episodes are well recognized causative or boosting factors. Environmental factors, including climate and ultraviolet light, are also presumed to be important in the provocation of acne [1, 6]. Hot and humid weather usually has a negative impact on acne. The effect of ultraviolet light is less obvious and more controversial. Some patients believe in the suppressive effect of sunlight on acne. The improvement may be caused by either the placebo effect or masking effect from sunlight tanning and erythema. By contrast, the effect of sunlight on acne is deleterious for some patients who complain from aggravation of acne lesions during summertime [10]. The mechanism probably primarily involves comedo formation.

Broadly, topical acne therapy can be divided into anti-comedonal and anti-bacterial (anti-inflammatory) agents. The presently reported comedolytic effect can be ascribed to the global formulation of the tested proprietary cream. Hence, compounds other than LHA may also participate in the overall *in vivo* effect seen in acne-prone patients. LHA basically belongs to the family of keratolytic and comedolytic agents [3, 18-20]. Resolving micromedones also decreases the follicular bacterial load. Loosening intercorneocyte binding may also be associated with an alteration in bacterial adherence inside the follicular openings [19]. This mechanism is not at risk of inducing bacterial resistance to antimicrobials [24].

In the present study design, the comedolytic effect was specifically assessed on early formed micromedones presumably induced by intense ultraviolet light exposure. As experienced in the control untreated group such follicular changes may spontaneously clear in a small percentage of acne-prone subjects within a 2-week period. It is inferred that some of these follicular cornified plugs are loosely adherent to the acro-infundibulum. The fact that the number and total size of the cornified follicular plugs decreased during treatment while their mean size remained unchanged means that these structures were eliminated as single block units rather than progressively thinned. This effect was achieved by twice daily applications when sun exposure was limited. Indeed, photodegradation of LHA may occur and limits its efficacy. Under the trial circumstances, the tolerance of the LHA formulation was excellent.

The proportion of the cornified follicular plugs turning to larger and adherent open comedones is unknown. When this process is prominent, microcomedonal acne should become manifest. In this acne progression pathway, the presently tested formulation is likely to be helpful in preventing seasonal outbreaks of acne. Once larger comedones are established, the efficacy of the LHA formulation is unknown compared to a

topical retinoid such as adapalene [25, 26].

Article accepted 2/12/2002

REFERENCES

- 1 Toyoda M, Morohashi M. Pathogenesis of acne. *Med Electron Microsc* 2001; 34: 29-40.
- 2 Piérard-Franchimont C, Piérard GE, Saint Léger D, Lévêque JL, Kligman A. Comparison of the kinetics of sebum secretion in young women with and without acne. *Dermatologica* 1991; 183: 120-2.
- 3 Piérard-Franchimont C, Piérard GE, Kligman A. Seasonal modulation of the sebum excretion. *Dermatologica* 1990; 181: 21-2.
- 4 Suh DH, Kwon TE, Youn JI. Changes of comedonal cytokines and sebum secretion after UV irradiation in acne patients. *Eur J Dermatol* 2002; 12: 139-44.
- 5 Sigurdsson V, Knulst AC, Van Weelden H. Phototherapy of acne vulgaris with visible light. *Dermatology* 1997; 194: 256-60.
- 6 Mills OH, Porte M, Kligman AM. Enhancement of comedogenic substances in ultraviolet radiation. *Br J Dermatol* 1978; 98: 145-50.
- 7 Piérard GE, Piérard-Franchimont C. Squamometry in acute photodamage. *Skin Res Technol* 1995; 1: 137-9.
- 8 Böhm M, Luger TA. The role of melanocortin in skin homeostasis. *Horm Res* 2000; 54: 287-93.
- 9 Petit L, Piérard-Franchimont C, Saint-Léger D, Loussouarn G, Piérard GE. Subclinical speckled perifollicular melanosis of the scalp. *Eur J Dermatol* 2002; 12: 565-8
- 10 Hjorth N, Sjolín KE, Sylvest B, Thomsen K. Acne aestivalis-Mallorca acne. *Acta Derm Venereol.* 1972; 52: 61-3.
- 11 Lévêque JL, Corcuff P, Gonnord G, Montastier C, Renault B, Bazin R, Piérard GE, Poelman MC. Mechanism of action of lipophilic derivative of salicylic acid on normal skin. *Skin Res Technol* 1995; 1: 115-

22.

12 Lévêque JL, Corcuff P, Rougier A, Piérard GE. Mechanism of action of a lipophilic salicylic acid derivative on normal skin. *Eur J Dermatol* 2002; 12: XXXV-VIII.

13 Corcuff P, Fait F, Minondo AM, Lévêque JL, Rougier A. A comparative ultrastructural study of hydroxyacids induced desquamation. *Eur J Dermatol* 2002; 12: XXXIX-XLIII.

14 Arrese JE, Piérard GE. El lipohidroxiacido y el envejecimiento cutaneo. *Arch Argent Dermatol* 1995; 45: 147-50.

15 Piérard GE, Nikkels-Tassoudji N, Arrese JE, Piérard-Franchimont C, Lévêque JL. Dermo-epidermal stimulation elicited by a beta -lipohydroxyacid: a comparison with salicylic acid and all-trans-retinoic acid. *Dermatology* 1997; 194: 398-401.

16 Avila Camacho M, Montastier C, Piérard GE. Histometric assessment of the age-related skin response to 2-hydroxy-5-octanoyl benzoic acid. *Skin Pharmacol Appl Skin Physiol* 1998; 11: 52-6.

17 Piérard GE, Kligman AM, Stoudemayer T, Lévêque JL. Comparative effects of retinoic acid, glycolic acid and a lipophilic derivative of salicylic acid on photodamaged epidermis. *Dermatology* 1999; 199: 50-3.

18 Piérard GE, Piérard-Franchimont C, Hermanns-Lê T. Hydroxyacids. In: Cosmeceuticals. Ed. P. Elsner, H. Maibach. Publ. M. Dekker, New York, 2000; 35-44.

19 Piérard GE, Rougier A. Nudging acne by topical beta-lipohydroxy acid (LHA), a new comedolytic agent. *Eur J Dermatol* 2002; 12: XLVII-L.

20 Piérard-Franchimont C, Piérard GE. Comedogenicity. In: Cosmetics. Controlled efficacy studies and regulations. Ed. P. Elsner, H.F. Merk, H.I. Maibach, Publ. Springer, Berlin, 1999; 268-274.

21 Piérard-Franchimont C, Piérard GE. Post-menopausal aging of the sebaceous follicle. A comparison between women receiving hormone replacement therapy or not. *Dermatology* 2002; 204: 17-22.

22 Piérard-Franchimont C, Petit L, Piérard GE. Skin surface patterns of xerotic legs: the flexural and

accretive types. *Int J Cosmet Sci* 2001; 23: 121-6.

23 Piérard-Franchimont C, Piérard GE. Beyond a glimpse at seasonal dry skin. A review. *Exog Dermatol*. 2002; 1: 3-6.

24 Kurokawa I, Nishijima S, Kawabata S. Antimicrobial susceptibility of *Propionibacterium acnes* isolated from acne vulgaris. *Eur J Dermatol* 1999; 9: 25-8.

25 Millikan LE. Adapalene: an update on newer comparative studies between the various retinoids. *Int J Dermatol* 2000; 30: 784-788.

26 Thiboutot D, Gold MH, Jarratt MT, Kang S, Kaplan DL, Millikan L, Wolfe J, Loesche C, Baker M. Randomized controlled trial of the tolerability, safety, and efficacy of adapalene gel 0.1 % and tretinoin microsphere gel 0.1 % for the treatment of acne vulgaris. *Cutis* 2001; 68: 10-19.