ORIGINAL ARTICLE

Double-blind clinical study reveals synergistic action between alpha-hydroxy acid and betamethasone lotions towards topical treatment of scalp psoriasis

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ABSTRACT

Objective A double-blind, single-site, split-face clinical study was organized and carried out in order to evaluate the efficacy, tolerability, and safety of a glycolic acid containing scalp lotion in conjunction with a betamethasone (as the 17-valerate) scalp application against conditions of psoriasis.

Background α-hydroxy acids (AHA) have been proposed as therapeutic modalities against skin exfoliative conditions such as ichthyosis, xeroderma, and psoriasis. AHAs are hereby clinically investigated as therapeutic modalities adjuvant to corticosteroids in order to diminish systemic and topical adverse side-effects most frequently associated with use of the latter.

Methods Twenty patients suffering from scalp psoriasis and other psoriatic conditions were included in a double-blind, split-face clinical study, using combinations of a 10% (w/w) glycolic acid scalp lotion, placebo lotion (excipients only), and a 0.1% (w/w) betamethasone scalp application, applied twice daily without any bandage for a period of 8 weeks. Clinical assessments were carried out by highly experienced physician evaluations based on a four-grade scale, prior to treatment and after 2, 4, 6 and 8 weeks.

Results Improvement was observed in all cases included in the study following treatment with the 10% glycolic acid lotion. However, when equal parts of the 0.1% betamethasone lotion were combined, most of the treated sites were healed. Moreover, the duration of treatment required for healing was in this case reduced to approximately half of that needed when the glycolic acid or the betamethasone lotions were used separately for treatment.

Conclusions The present clinical study demonstrates for the first time that the effective and well tolerated therapeutic efficacy of glycolic acid scalp lotions is enhanced when used in conjunction with a 0.1% betamethasone scalp application against scalp psoriasis. This potential offers the practising dermatologist with novel treatment modes against severe skin conditions by combining topical corticosteroid with exfoliative agent therapy.

Key words: alpha-hydroxy acid, AHA, scalp lotion, betamethasone, psoriasis, corticosteroids

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Introduction

Topical glucocorticoids are among the dermatological treatments used most frequently today. This is due to their prominent therapeutic efficacy against inflammatory skin as well as other severe skin conditions. Indeed clinical studies have reported previously the beneficial therapeutic effects of topical corticosteroid application towards treatment of scalp psoriasis,[1] and seborrhoeic and atopic dermatitis of the scalp.[2] It has also been demonstrated that for the betamethasone 17-valerate

corticosteroid, the topical drug availability increases dramatically when used in the scalp application formulation in comparison to cream, lotion and ointment formulations.[3] Parameters such as the latter, are particularly important as corticosteroid use is also associated unavoidably with adverse systemic and topical side-effects. Therefore, any attempt to develop modern therapies should involve consideration of clinical effectiveness, drug deposition and skin tolerance response.

The most common adverse effect following topical treatment of scalp psoriasis using corticosteroids, reported in an extensive multicentre clinical study involving 474 patients, was lesional and perilesional irritation which occurred significantly more with calcipotriol than with betamethasone.[1] Also, cutaneous atrophy and facial telangiectasia have been associated with long-term application of a topical corticosteroid to the scalp.[4] Systemic adverse effects thought to be involved with topical corticosteroid use, include adrenal suppression. Two clinical trials performed in patients with psoriatic erythroderma and psoriasis treated with corticosteroids, including the one employed in the present study (betamethasone 17-valerate), reported occurrence of adrenal suppression.[5] Hence, as has been stressed before,[6] therapeutic modalities with an increased benefit–risk ratio are needed and research on new drugs no longer focuses on more active drugs but safer ones. In view of this, we undertook the present clinical study, investigating the efficacy and tolerance of combinations between scalp lotions containing α-hydroxy acids (AHAs) and betamethasone scalp application.

In fact, the only existing study in the literature investigating both corticosteroids and AHAs,[7] reported on the use of an AHA salt (ammonium lactate) to alleviate the adverse conditions procured from potent topical corticosteroid therapy such as cutaneous atrophy, mainly by increasing the thickness of the epidermis and by synthesis of glycosaminoglycans. For quite a few years now AHAs have been used in cosmetic dermatology applications,[8] primarily as highly concentrated glycolic acid lotions (50–70%) for intensive chemical peeling treatments.[9] During the last decade though, a widespread use of low AHA concentration cosmetic formulations was evidenced claiming to act against the loss of elasticity and slow metabolic activity found in aged skin.[10] Moreover, AHA formulations have also been used as therapeutic agents of pathological skin conditions such as photodamaged skin[11,12] hyperpigmentations (chloasma, melasma),[13,14] and other hyperkeratotic skin conditions (xeroderma, ichthyosis).[8,15] The present clinical study aimed at investigating: i) the clinical effectiveness and tolerance of a 10% (w/w) AHA-containing scalp lotion towards treatment of scalp psoriasis; and ii) the effect of combinatory treatment using the AHA-containing lotion and 0.1% (w/w) betamethasone scalp application, relative to treating patients with scalp psoriasis using betamethasone alone.

Materials and methods

The formulations included in the study were a scalp lotion containing glycolic (5% w/w) and lactic (5% w/w) acid at pH 3.5, a lotion containing excipients only (ethanol 40%, propylene glycol 20%, deionized water 40% w/w), and a 0.1% (w/w) betamethasone scalp application (17-valerate, Betnovate™). The AHA and excipient lotions were provided by the R & D Laboratories of Farmeco Co. (Athens, Greece). In order to carry out a split-face study, the patients applied two different formulations at each half-side of their face or body, twice a day without any bandage.

The double-blind clinical trial was organized and executed at the outpatient dermatology research clinic, Hospital for Skin and Aphrodisiac Diseases, School of Medicine, Aristotle University of Thessaloniki, Greece. A total number of 20 adult patients (17 men and three women) participated in the study suffering from scalp psoriasis and seborrhoeic psoriasis. Cases of severely irritated, highly inflamed skin were not enrolled in the study, as AHAs exaggerate irritation of such conditions, thus their use is not recommended. The clinical trial commenced in October 1994 and was concluded February 1997. Treatment was regularly monitored by highly experienced physician evaluations of efficacy and irritation, and treated areas were photographed prior to treatment and after 2, 4, 6, or 8 weeks, according to therapeutic progress observed. All formulations were coded at the beginning and during the clinical study, and only following recording of all final assessments concerning efficacy and tolerance were they decoded. Glycolic and lactic acids were chosen for the study, as these are the most effective of the AHA molecules, and are therefore most prone to lead to irritation and other adverse side-effects.

Results

Assessment of the scalp lotion formulations' clinical efficacy was based on two parameters, namely therapeutic effect and required duration to procure that effect. Diagnosis from experienced dermatologists evaluated the lotion's clinical performance on the four-grade scale shown as legend in fig. 1. The data are presented as mean ± standard error of mean; statistical evaluations were carried out using the two-tailed Student's *t*-test. The results observed at the end of an 8-week treatment period using the lotions and their combinations are depicted (fig. 1). The AHA-containing lotion when used alone for treatment, in a total number of eight diseased sites, produced 'markedly improved' effect in seven of them, and 'slightly improved' in the remaining site. On the other hand, when the excipients-only lotion, containing ethanol, propylene glycol, and water (40/20/30% wt/wt) was used, in most patients only a 'slightly improved' effect was observed. Representative illustration of the effects mentioned above is

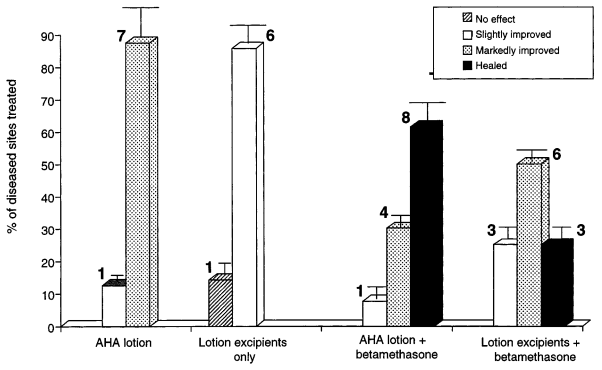

fig. 1 Clinical performance of lotion formulations following an 8-week treatment period. It has to be noted that the results presented as percentages (%) of the total number of diseased sites to which the lotion treatments were applied were evaluated of statistical significance ($P < 0.001$–0.002), however, the total number of diseased sites where treatment was applied can be considered rather low

offered in fig. 2. The beneficial therapeutic effect of AHA lotion (a and b) compared to the lotion containing excipients only (c and d) is evident for the same patient, as shown.

The most interesting effects though were obtained when equal parts of 0.1% (w/w) betamethasone scalp application were added to the lotions mentioned above. Treatments using lotion containing AHAs with the steroid compared to treatments using steroid with the excipient lotion demonstrate an apparent synergistic action between AHA and betamethasone towards scalp psoriasis treatment, resulting in most 'healed' sites ($8 \pm 2/13$) than any other combination (fig. 1). Moreover, the therapeutic synergy between the AHA and the corticosteroid was also evident as end-effects were obtained in almost half the required period (approximately 4 weeks) of that required in the case of using either AHA or betamethasone as separate treatments (approximately 8 weeks). It has to be mentioned that no systemic or topical side-effect was experienced by the patients, or any irritation effect observed during diagnosis by any of the patients for any lotion formulation.

Discussion

In the present clinical study for the first time results indicate the synergistic action between an AHA-containing scalp lotion and a betamethasone scalp application towards therapy of scalp psoriasis. This skin condition was chosen to be studied as it has been described as an ideal clinical model to specifically evaluate corticosteroid potency because the ability to perform within-patient comparisons of the treatment (similar to those described in fig. 2) permits meaningful comparisons with a relatively small sample size.[16] Moreover, the results of bilateral comparisons in psoriasis agreed with those of *in vitro* vasoconstrictor assays, contrary to other skin conditions, such as eczematous dermatoses.[16] According to such studies, even though the number of patients enrolled in the present clinical study can be considered relatively small, conclusions produced may confidently be considered of statistical validity.

α-Hydroxy acids have been clinically evaluated as effective therapeutic agents for a variety of skin exfoliative diseases in the past. Here, the observed therapeutic efficacy of glycolic and lactic acid containing lotions at 10% w/w and pH 3.5 against scalp psoriasis was considered efficient, particularly for non-drug, exfoliative agents such as AHAs and at the low concentrations used. It seems that further more systematic investigations may well improve the effectiveness obtained presently by varying such AHA lotion formulation parameters as AHA molecule, concentration, and pH level. Another interesting point from the present clinical study is that the role of the lotion excipients has been determined (fig. 1). The fact that 'slightly improved' effects were obtained for the majority of psoriatic scalp areas treated with the excipients, determines the extent to which traditional skin penetration enhancers like polypropelene glycol and ethanol contribute to therapeutic effects.

The 'markedly improved' and 'healed' effects observed in the vast majority of treated psoroasis sites from combining the corticosteroid molecule with the AHA and excipient lotions were expected. What was not expected however, and has not been reported previously in the literature, was the evidently more effective AHA-betamethasone combination compared to the excipient-betamethasone. AHAs recently have been at the centre of controversy primarily due to their yet unresolved and inadequately described mode of action both as skin penetration enhancers[17] and as skin disorder treatment modalities.[15]

AHAs certainly penetrate the epidermal layers, provoking an increase in stratum corneum turnover. Recent *in vitro* studies evaluating the effect of glycolic acid on cultured human dermal fibroblasts[18] evidenced increased cell proliferation and collagen production in response to glycolic acid in a dose-dependent manner, suggesting functional activation of fibroblasts. The latter *in vitro* data were also verified *in vivo* by a different group,[19] concluding that a 6-month treatment of photoaged skin (forearm) with a 25% wt/wt glycolic, lactic or citric acid led to an approximate increase of 25% in skin thickness, followed by increased density of collagen. A possible mechanism of AHA molecular action has been proposed recently by other investigators using *ex vivo* human stratum corneum,[11] concluded that the occurring exfoliation of the stratum corneum outermost layer (stratum disjunctum) and the observed enhanced desquamation did not disrupt the stratum corneum barrier structures. Rather, interestingly, they suggest that glycolic acid molecules target the stratum disjunctum desmosomes (deeper layer – stratum compactum – desmosomes found unaffected), leading to enhanced desmosomal breakdown and promoting loss of corneocyte cohesion and desquamation.

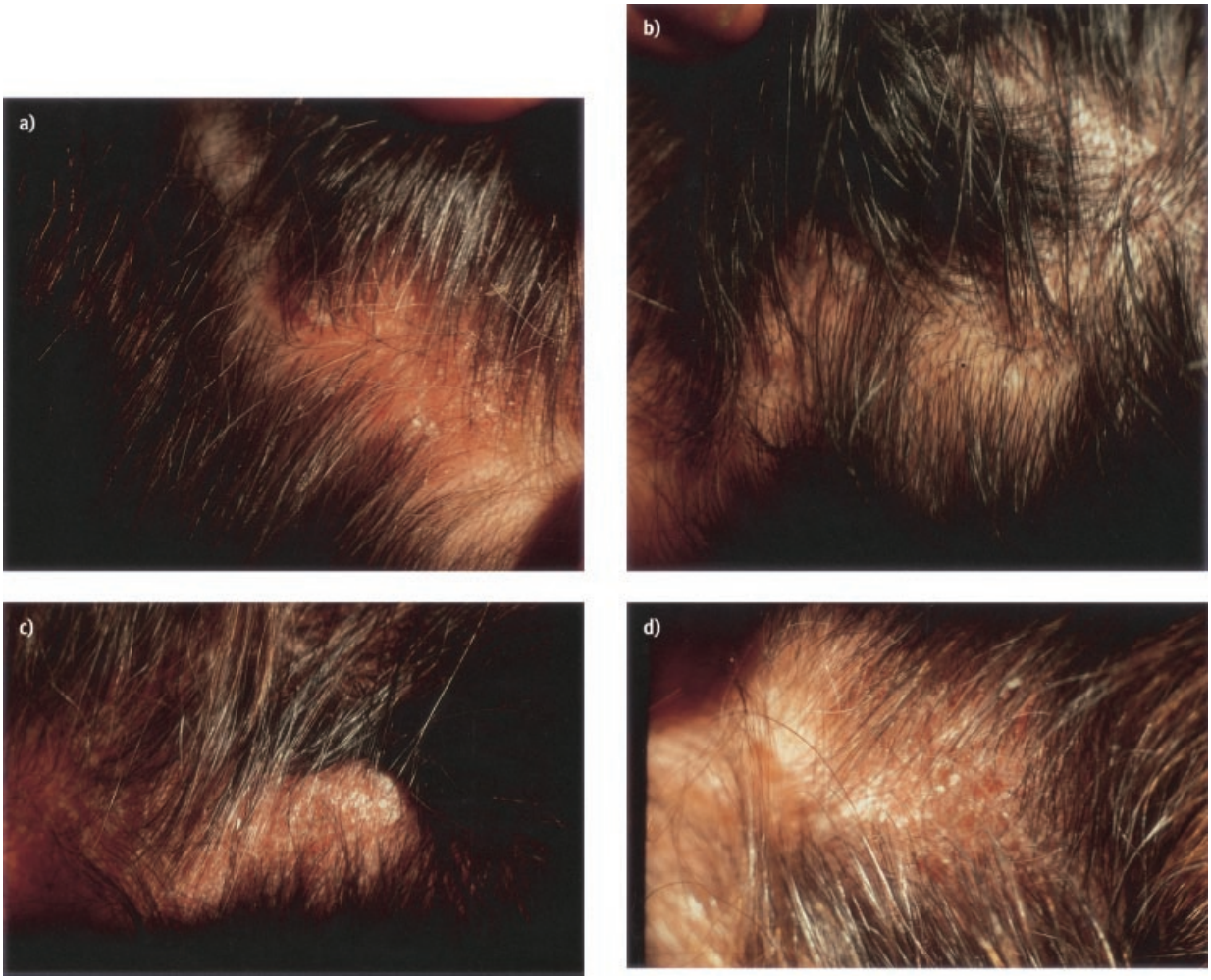

fig. 2 Half-side of scalp psoriatic patient a) before and b) after the 8-week treatment using the glycolic-lactic acid (10% w/w) scalp lotion. Other half-side of the same patient c) before and d) after the 8-week treatment using the lotion containing ethanol, propylene glycol, and water (40/20/30% wt/wt)

The present study, by combining AHA scalp lotion with betamethasone scalp application denotes that: i) α-hydroxy acids are indeed beneficial towards treatment of severe scalp conditions; ii) by combining α-hydroxy acids, or perhaps other exfoliative agents, with corticosteroids, therapy of severe dermatological conditions may well be achieved by using considerably reduced doses of the latter. Therefore, by decreasing topical steroid availability (thus deposition), their concomitant adverse effects may be contained effectively with equally, or even improved as fig. 1 shows, potent therapy; and iii) safer and better tolerated steroid treatments become more feasible when combined with AHA molecules due to the significant reduction in the required duration of treatment in order to reach therapeutic effect. Lastly, the fact that all 20 patients enrolled in this study tolerated the lotions for the 8-week period without any irritation or stinging response, further encourages use of such combinatory therapeutic treatments.

Further studies are under way in this laboratory comparing the therapeutic effect of particular AHA molecules in combination with corticosteroids towards treatment of a variety of dermatological conditions. However, more studies will certainly be needed from others too, until we may be able to efficiently describe the molecular interactions between the AHAs and skin components, in order to help resolve the controversy surrounding their action and rationalize on the extent of their therapeutic capabilities.

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