NOVEL RETINOID ESTER IN COMBINATION WITH SALICYLIC ACID FOR THE TREATMENT OF ACNE

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ABSTRACT

Retinoids (RC), alpha hydroxy acids (AHA), and salicylic acid (SA) have therapeutic benefit in acne treatment through differing mechanisms of action. It is theorized that optimal acne improvement could be achieved by combining the RC induced normalization of cellular differentiation, AHA induced exfoliation in hydrophilic areas, and SA induced exfoliation in lipophilic areas. The AHA and RC compounds have been combined in a biologically designed molecule, known as an AHA Retinoid Conjugate (AHA-RC; chemically known as ethyl lactyl retinoate), delivering both lactic acid (AHA) and RC in a time-released hydrolytic manner designed to reduce retinoid associated irritation. A 27 subject 8-week clinical trial in subjects with mild to moderate acne was conducted using a 3-product regimen consisting of a twice daily cleanser (7.8% l-lactic acid, 2% SA), a twice daily acne serum (0.1% AHA-RC, 2% salicylic acid & 10.4% l-lactic acid) and a broad spectrum SPF 50+ sunscreen as needed. Investigator counts of total inflammatory (papules, pustules) and non-inflammatory (open comedones, closed comedones) lesions revealed a statistically significant reduction in inflammatory lesion counts ($p=0.006$) and non-inflammatory lesion counts ($p=0.015$) after 4 weeks of use. Improvement continued into week 8 with highly statistically significant ($p<0.001$) reductions in inflammatory and non-inflammatory lesions. Thus, the combination of lactic acid, SA and the novel AHA-RC produced acne improvement after 4 weeks with continuing cumulative improvement at 8 weeks. AHA-RC represents a new molecule combining several mechanisms of action to achieve acne improvement.

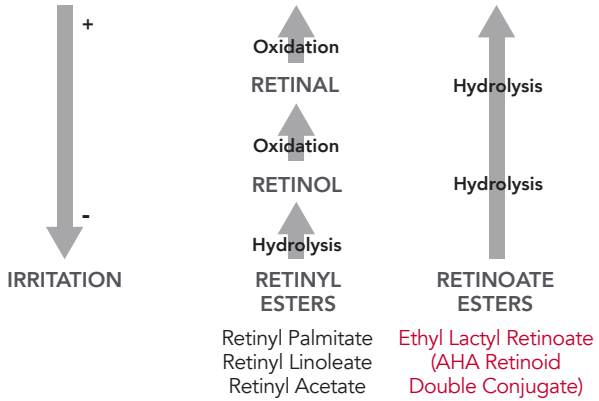
INTRODUCTION

Topical therapies serve as the frontline treatment in all but the most severe cases of acne vulgaris due to their relatively low cost and ease of use. Compliance is often an issue with topical acne therapies,[1] especially those with associated unpleasant side effects such as stinging and burning, redness, or drying and flaking of skin.

Retinoid compounds (RC; vitamin A and its derivatives) are heavily studied and used but still not well understood; they are commonly used to treat acne, photodamage, and other skin conditions due to the range of biological effects (normalization of melanocyte function, immunomodulation, regulation of skin cell metabolism and cellular turnover, thickening of the epidermis, increases in dermal fibroblast production and activity, stimulation of neocollagenesis, and an increase in the height of rete ridges and the number of dermal papillae[2–5]). When treating acne they serve to normalize cell differentiation and inhibit key immunity factors.[6] Associated irritation makes topical use somewhat problematic as it may affect compliance.[7] Alpha hydroxy acids (AHA) are nontoxic, organic acids (e.g. glycolic acid, lactic acid, malic acid, etc.) consisting of a carboxylic acid functional group with a hydroxyl group (alcohol) on the adjacent (alpha) carbon atom; some, such as lactic acid, are present within the body.[8] Harnessed effects include moisturization, exfoliation, and dermatologic indications involving abnormal keratinization. Their safety, moisturization, and exfoliant properties make them ideal for topical use. Salicylic acid (SA), a beta hydroxy acid (or BHA), is one of five FDA cleared OTC therapies for acne and present in numerous topical formulations. Bacteriostatic and kerolytic properties as well as correction of abnormal shedding of cells have been noted[9] but require continuous use; SA does not affect sebum production or kill bacteria. It is theorized that optimal acne improvement could be achieved by combining the RC induced normalization of cellular differentiation, AHA induced exfoliation in hydrophilic areas, and SA induced exfoliation in lipophilic areas.

Unfortunately, therapeutic doses of topically applied retinoids frequently cause skin irritations that interfere with treatment. Figure 1 shows the relationship between commonly used retinoids and general irritation level, and the process by which they are converted from one form to another. Esters are molecules made by reacting an organic carboxylic acid and an alcohol through a condensation reaction, and typically provide increased stability and reduced irritation over the parent compounds. Attempts to reduce retinoid irritation by esterifying Vitamin A with fatty acids or other common organic acids such as palmitic acid or acetic acid to produce 'retinyl' esters (e.g. retinyl palmitate and retinyl acetate) also result in reduced efficacy.

Figure 1. Vitamin A Derivatives, Method of Conversion and Irritation Potential



Vitamin A Derivatives, Method of Conversion and Irritation Potential

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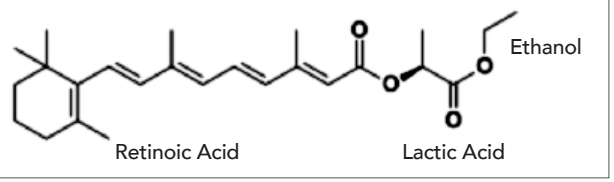
A NEW AHA-RETINOID DOUBLE CONJUGATE MOLECULE

Although technically considered carboxylic acids and alcohols, reactions where AHAs are reacted as "alcohols" are not common. Retinoate esters can be engineered by combining AHA (as the alcohol) with vitamin A acid. Beneficial results include increased stability and reduced irritation when compared to the parent compound, but esterification often detrimentally affects efficacy. A bioengineered retinoid ester, ethyl lactyl retinoate (AHA retinoid conjugate, or AHA-RC), is the first double conjugate retinoid to deliver both AHA and RC to skin on a hydrolysis-based time released mechanism biologically designed to be efficient and minimally irritating to patients. A molecular model of this novel ester is presented in Figure 2.

Figure 2. Molecular diagram of AHA retinoid conjugate (AHA-RC).



Molecular diagram of AHA retinoid conjugate, or AHA-RC.

STUDY PURPOSE

The purpose of this 8 week, prospective pilot study was to evaluate efficacy and tolerability of a twice daily, three product skincare regimen using the bioengineered AHA retinoid conjugate ester plus SA in patients with acne.

STUDY METHODS

Women (n=27) aged 40–65 years (mean 52±6.20) presenting with a minimum of 15 inflammatory acne lesions and a minimum of 15 non-inflammatory lesions were enrolled. The study was conducted under current Good Clinical Practices (cGCP) guidelines using an independent investigational review board (IIRB) -approved protocol. After initial screening (Days -10 to -7) during which informed consent, medical history, inclusion/exclusion criteria review, initial endpoint assessment, and other pre-screening activities were performed, enrolled subjects were instructed to discontinue use of facial products excepting dry mineral foundation and eye makeup for 7 to 10 days prior to beginning the study ("washout" period). Pre-screening was reviewed at baseline (day 0) with re-assessment of initial endpoint evaluations including a comprehensive lesion count (inflammatory lesions, non-inflammatory lesions, papules, pustules, open comedones and closed comedones). Baseline digital photographs were obtained. Product was dispensed with clear instructions for proper use.

The three-product regimen included cleanser (7.8% l-lactic acid, 2% BHA), active topical (0.1% AHA-RC, 10.4% l-lactic acid, 2% BHA), and broad-spectrum sunscreen (SPF 50+); subjects were to apply the topical after cleansing in the morning and evening. Sunscreen was to be applied after morning application of product and as needed throughout the day. Subject diaries were included to promote compliance and obtain subject commentary or observations.

Digital photography and visual expert grading of endpoints were performed at week 4 and week 8 follow-up; acne was evaluated via comprehensive lesion count (inflammatory lesions, non-inflammatory lesions, papules, pustules, open comedones and closed comedones). Secondary endpoints of Dryness/Flaking, Fine Lines/Wrinkles, Dyschromia, Stinging/Burning, and Erythema/Redness were evaluated by the investigator on a 0-5 scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=moderately severe, 5=severe). Global improvement was measured on a 0-4 scale (0=no improvement, 1=minimal improvement, 2=mild improvement, 3=moderate improvement, 4=marked improvement). Adverse events were recorded along with any concomitant medication information as well. Subject diaries were collected (and new ones dispensed) at week 4; at week 8 (Day 56) subject diaries and any remaining product were collected.

The primary clinical endpoint was the comprehensive lesion count with comparisons made at the week 4 and week 8 visits against baseline evaluations. Similar comparison was made for secondary endpoints. Data were analyzed via Mann-Whitney test using the cutoff of $p<0.05$, with $p<0.001$ denoting high significance.

RESULTS

Of enrolled subjects (n=27), 24 completed the study. Two subjects discontinued the study due to irritation adverse events; there were no serious adverse events, and one subject was lost to follow up.

There was a statistically significant reduction in inflammatory and non-inflammatory lesion counts at week 4, with highly statistically significant reduction seen by week 8. Specifically, there was a statistically significant reduction in papules ($p<0.001$) and closed comedones ($p<0.001$) at week 8. Table 1 shows percentage of improvement with corresponding p values; Figure 3 graphically demonstrates study results. Data indicates strong, significant improvement in acne with proper use of the AHA-RC plus SA topical. Reductions in lesion counts across the board were notable and, for the most part, highly significant.

For secondary endpoints, statistically significant increase in facial stinging seen at week 4 subsided to statistical insignificance by week 8; statistically significant improvement (29% on average) was noted in fine lines, and improvement in global appearance (average 57%) was more profound. This is particularly important in treating adult female acne, one of the most prevalent forms of acne. Statistically significant increases were not observed in dryness or erythema, further attesting to the tolerability of the acne treatment. Figures 4 & 5 demonstrate typical visible results demonstrated in the study.

Table 1: Acne Lesion Percent Improvement, Baseline to Week 8

LESION TYPE	Inflammatory	Non-inflammatory	Papules	Pustules	Open Comedones	Closed Comedones
% IMPROVEMENT	64	55	67	37	87	51
P VALUE*	<0.001	<0.001	<0.001	0.475	0.187†	<0.001

*p<0.05 denoted statistical significance, p<0.001 denoted high statistical significance
†Open comedones were only present in two patients, which may explain the lack of statistical significance despite an obviously large percentage of improvement.

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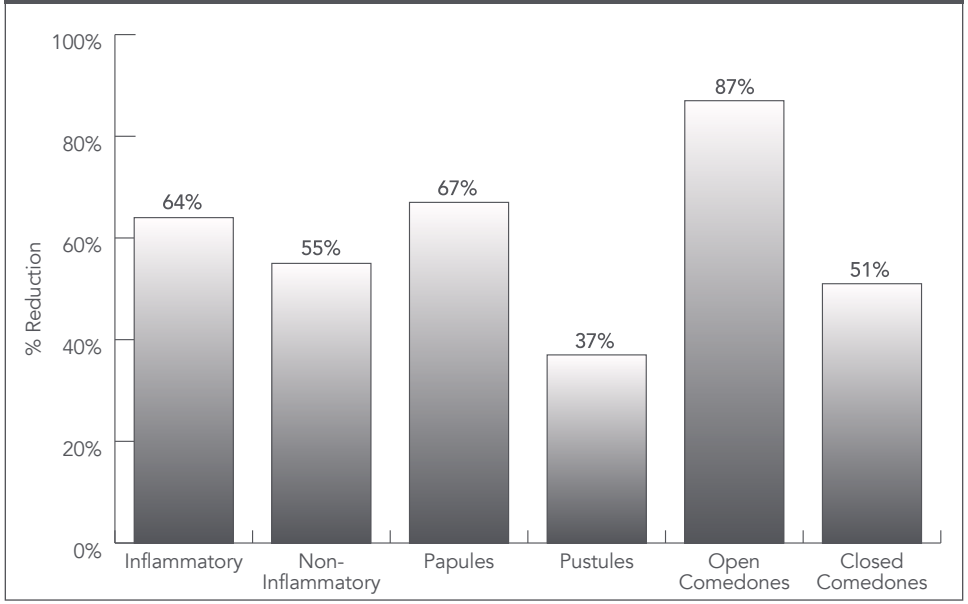
Figure 3. Comparison of Percent Improvement in Acne Lesion Count, Baseline to Week 8



CONCLUSION

The three product regimen (AHA-RC plus SA) was shown to be safe and effective for treatment of acne; statistically significant reductions in both inflammatory and non-inflammatory acne lesion counts were noted. Significant improvement to overall skin quality was also observed.

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Figure 4. SUBJECT 18: day 0 vs 8 Weeks

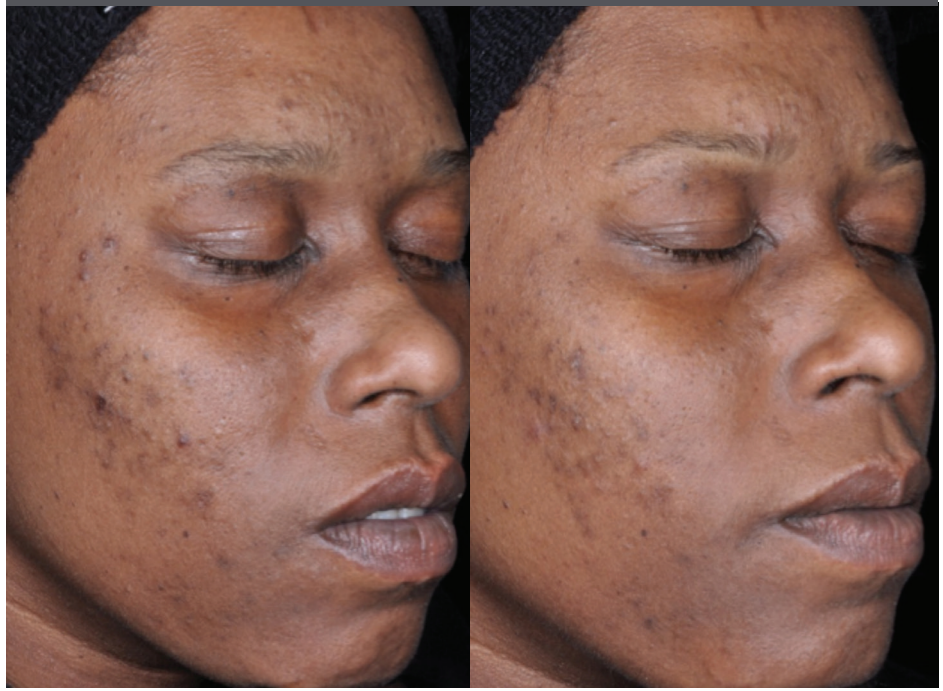

Figure 5. SUBJECT 21: day 0 vs 8 Weeks