

Efficacy and tolerability of a double-conjugated retinoid cream vs 1.0% retinol cream or 0.025% tretinoin cream in subjects with mild to severe photoaging

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Summary

Background: Topical retinoids are used to treat the visible signs of photoaging. While efficacious, they are irritating.

Objective: Evaluate the effectiveness and tolerability of a double-conjugate retinoid cream (AlphaRet Overnight Cream; AHA-Ret) in improving visible signs of photoaging vs 1.0% retinol or 0.025% tretinoin.

Methods: A 12-week, split-face, randomized trial was conducted in 48 female subjects, aged 30-65 years with mild to severe photodamage. AHA-Ret was applied to one side of the face and either retinol (n=24) or tretinoin (n=24) to the other side (PM). Expert blinded evaluation of images and Nova measurements occurred at 4, 8, and 12 weeks. Tolerability was assessed throughout the study.

Results: Forty-seven subjects completed the study. AHA-Ret demonstrated significant reductions in average severity from baseline: Fine Lines/Wrinkles ($P<.001$; all time points); Erythema ($P=.004$, $P<.0001$; 8 and 12 weeks, respectively); Dyschromia ($P<.0001$; all time points); Skin Tone ($P<.0001$; all time points), and Pore Size ($P=.035$, $P<.0001$; 8 and 12 weeks, respectively). AHA-Ret induced less Erythema vs retinol at 8 ($P=.008$) and 12 ($P<.02$) weeks. AHA-Ret was noninferior to prescription tretinoin in all categories at 4 and 8 weeks, and for Fine Lines/Wrinkles, Erythema, Dyschromia, and Skin Tone at 12 weeks. Improvements in Hydration occurred at every time point with AHA-Ret only ($P<.04$, $P<.03$, $P<.01$). Less irritation was reported with AHA-Ret vs retinol or tretinoin.

Conclusions: Treatment with a double-conjugate retinoid cream demonstrated early reductions in photodamage and improvements in Hydration. AHA-Ret induced less Erythema vs retinol and was more tolerable vs retinol and tretinoin.

KEYWORDS

alpha hydroxy acids, photoaging, retinoid, Tretinoin

1 | INTRODUCTION

Changes to skin are among the most visible signs of aging. Photodamage or extrinsic aging, resulting from sun exposure and ultraviolet radiation, accelerates the natural changes of aging and is a primary cause of premature aging of the skin. Intrinsic or chronological aging markedly impacts skin barrier function and is multifactorial.¹ Reduction in the number of melanocytes in the skin, as well as an increase in the size of melanocytes, results in thinner, paler, and more translucent-looking skin. Sebaceous glands produce less oil, causing the skin to become drier. Reductions in collagen type I manifest as fine lines, wrinkles, and skin laxity. Changes in connective tissue cause elastosis, reducing skin strength and elasticity, facilitating development of irregular elastin structure. Collagen and elastin provide structural support to skin pores; however, the loss of both collagen and elastin enable pores to stretch and sag around their edges, making them appear larger. Notably, the rate of cell turnover and shedding of dead skin cells naturally slows with age; dead cells accumulate on the outer surface of the skin, giving the complexion a dull, sallow look.² Visible effects of photodamage may manifest as fine lines and wrinkles, erythema, pigmentary and skin tone changes, a larger appearance in pore size, and skin sagging and crepiness.

Topical agents are often utilized to promote exfoliation and facilitate cell turnover. This removes the top layer of dead skin that dulls the skin's appearance and enhances cell renewal rate, improving the appearance of the skin and the visible signs of photoaging. Both retinoid-containing derivatives (prescription and nonprescription) and alpha hydroxy acids (AHAs) are established treatments which have been shown to effectively improve visible skin changes associated with aging.²

Retinoids and AHAs are often referred to as "gold standard" ingredients due to their ability to rejuvenate the skin by influencing the rate of cell turnover and exfoliation. AHAs (especially lactic and glycolic acid) impart benefits to the skin by both fostering skin moisturization and promoting skin exfoliation.^{2,3} AHAs exfoliate the surface of the skin, facilitating skin turnover and renewal of the stratum corneum, improving skin texture, fine lines and wrinkles, and pigmentation.⁴ At lower doses, AHAs modulate the surface of the skin and epidermal changes; at higher concentrations they influence the epidermal and dermal layers.^{4,5} Additionally, lactic acid has a specific glycoprotein-binding site on the fibroblast that induces moisture retention in the dermis and epidermis. Increasing skin moisture retention increases epidermal and dermal volume, thus reducing fine lines and wrinkles and increasing brightness of the skin.² As the smallest AHA molecule, glycolic acid penetrates the skin more readily than other AHA molecules and has the greatest bioavailability. Glycolic acid also has both anti-inflammatory and antioxidant effects, and is safe to use with all Fitzpatrick skin types.^{3,6}

Retinoids increase cellular mitosis, stimulate collagen production to thicken and repair the epidermis, normalize melanocyte function, and regulate skin cell metabolism and cellular turnover, thereby improving pigmentation, skin texture and roughness, and fine lines and wrinkles.^{2,7-10} Tretinoin is a prescription strength retinoid

approved by the US Food and Drug Administration (FDA) for acne and for the mitigation of fine facial wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin. Prescription strength tretinoin affords the most potent retinoid effects, but often results in limited utility and decreased adherence due to irritation reactions (ie, burning, scaling, and dermatitis).¹¹ Although early studies showed no statistically significant difference (clinically or histologically) in efficacy between lower (0.025%) and higher (0.1%) strength tretinoin on photodamaged skin, there are significantly greater adverse effects associated with the higher strength formulation.¹² While the "no pain, no gain" adage may be more acceptable to patients when associated with chemical peels or device-based procedures in an attempt to improve photodamaged skin, side effects from topical agents can result in poor compliance and/or treatment discontinuation.

Tran and colleagues demonstrated that the combination of an AHA (glycolic acid) with a retinoid regimen facilitated better bioavailability and greater delivery of the retinoid while reducing or preventing tolerability issues.¹³ In an effort to mitigate the tension that currently exists between efficacy and tolerability, a bioengineered, double-conjugated molecule (AlphaRet Overnight Cream; AHA-Ret) has been developed that effectively combines a potent retinoid plus lactic acid. Through nontraditional, double hydrolysis, the ester bonds that join these two molecules together are broken in the skin by naturally occurring enzymes. The process of breaking these double bonds gradually releases the retinoid and AHA into the skin, maximizing efficiency and minimizing potential irritation. The unique mechanisms of action of the retinoid and lactic acid work synergistically to promote skin rejuvenation. Designed to optimize delivery of the beneficial properties of both an AHA and a retinoid, double conjugation helps to increase molecular stability, reduce irritation, and improve passage through the skin.

The purpose of this 12-week study was to evaluate the effectiveness and tolerability of a double-conjugated retinoid cream in improvement in the appearance of photoaging in comparison with either a 1.0% cosmeceutical retinol cream (retinol) or a prescription (generic) 0.025% tretinoin cream.

2 | SUBJECTS AND METHODS

2.1 | Subjects

Female subjects, 30-65 years of age, with evidence of mild to severe facial photoaging with no known medical conditions that, in the investigator's opinion, may interfere with study participation, were enrolled in this trial. Subjects committed to practicing moderate sun avoidance. Exclusion criteria included any dermatologic disorder that may interfere with evaluation, such as severe acne vulgaris, acne conglobate, acne fulminans, facial seborrheic dermatitis, or systemic lupus erythematosus; no known hypersensitivity to any of the ingredients in the study products; use of concurrent (topical or oral) therapy with any medication that may interfere with evaluation (such as a prescription retinol product); use of any skincare products or procedures that may interfere with evaluation (eg, use of a

nonprescription retinoid or retinol product within the prior 4 weeks); pregnancy or lactating during the study period; and must be able and willing to comply with the protocol requirements and sign a written informed consent.

2.2 | Methods

The study was conducted by a board-certified dermatologist under Independent Review Board (IRB; Chesapeake IRB, Columbia, MD, USA) approval in conjunction with current Good Clinical Practices (cGCP) guidelines. The initial screening visit, which may have been combined with the baseline visit, included obtaining informed consent, medical history, demographics, and concomitant medication history; along with inclusion/exclusion criteria review. Enrolled subjects were instructed to apply study products to clean skin, once daily in the evening for 12 weeks. Subjects were instructed to use sunscreen in the morning and a moisturizer, followed by use of their routine makeup products (if applicable). In addition to study products, cleanser, moisturizer, and a sunscreen were provided to ensure consistency of treatment regimen throughout the study period. AHA-Ret was provided by the sponsor in individual containers containing only lot and batch numbers. Comparator product(s) were provided in commercial packaging to keep from contaminants and for stability purposes.

In a split-face design, subjects were instructed to apply AHA-Ret and a comparator (retinol or tretinoin) according to their randomization assignment. AHA-Ret was applied to one side of the face and either tretinoin or retinol was applied to the opposite side of the face. Enrolled subjects were randomized to Group A1 (AHA-Ret on the right side, tretinoin on the left side), Group A2 (tretinoin on the right side, AHA-Ret on the left side), Group B1 (AHA-Ret on the right side, retinol on the left side), or Group B2 (retinol on the right side, AHA-Ret on the left side) (Figure 1).

2.3 | Study endpoints and assessments

The primary endpoint was blinded expert evaluations of Fine Lines/Wrinkles, Dyschromia, Erythema, Skin Tone Degradation, and Pore Size (scale range: 0=none, 1=minimal, 2=mild, 3=moderate, 4=moderately severe, 5=severe) at baseline, 4, 8, and 12 weeks based on

digital images using the Canfield Scientific VISIA-CR system. Global Improvement was assessed at 4, 8, and 12 weeks.

Secondary endpoints included Nova moisture meter measurements and subject completion of a 21-item self-assessment questionnaire obtained at 4, 8, and 12 weeks. Adverse events (AEs) were collected throughout the study.

2.4 | Statistical analysis

An independent statistician analyzed data using nonparametric Mann-Whitney and Wilcoxon signed-rank tests to determine statistical significance for respective parameters relative to baseline, across all three groups and examined a noninferiority hypothesis.

3 | STUDY RESULTS

3.1 | Study population

Forty-seven subjects with an average age of 55 years and Fitzpatrick skin type II completed the study. One subject was lost to follow-up.

3.2 | Efficacy

3.2.1 | Expert evaluation

AHA-Ret demonstrated statistically significant reductions from baseline in average severity of Fine Lines/Wrinkles, Dyschromia, and Skin Tone Degradation at all time points, and statistically significant reductions in Erythema and Pore Size were achieved at 8 and 12 weeks (Figure 2).

Fine lines/wrinkles

There was a statistically significant reduction in average severity scores from baseline in Fine Lines/Wrinkles for AHA-Ret at all time points: 14.3% at 4 weeks, 23.8% at 8 weeks, and 33.3% at 12 weeks ($P=.0001$, all) (Figure 3A). Retinol did not achieve statistically significant differences in Fine Lines/Wrinkles at 4 weeks, while tretinoin achieved statistical significance through week 12 ($P=.02$, $P=.002$, and $P=.0001$, respectively).

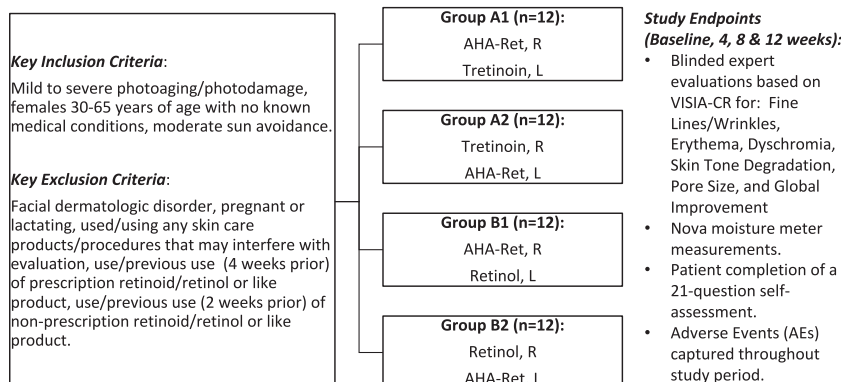
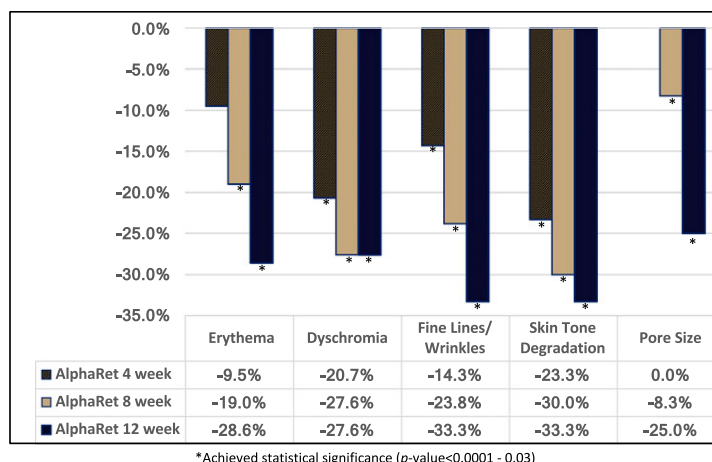


FIGURE 1 Methods and design

FIGURE 2 AHA-ret average percent reduction from baseline in severity



Dyschromia

There was a statistically significant reduction in average severity scores from baseline in Dyschromia for AHA-Ret at all time points: 20.7% at 4 weeks, 27.6% at 8 weeks, and 27.6% at 12 weeks ($P<.0001$, all). AHA-Ret was statistically superior to retinol in reduction in average severity score from baseline for Dyschromia at week 4 ($P<.0185$). Tretinoin achieved statistical significance through week 12 ($P=.008$, $P<.0001$, and $P<.0001$, respectively).

Erythema

AHA-Ret induced statistically significantly less Erythema in average severity scores from baseline by 19% ($P=.004$) at 8 weeks and by 28.6% ($P<.001$) at 12 weeks (Figure 3B). AHA-Ret was statistically superior to retinol in reduction in average severity score from baseline for Erythema at 8 and 12 weeks ($P=.008$ and $P=.02$, respectively). Retinol did not achieve statistical significance from baseline at any time point and demonstrated increases in Erythema over baseline at 4 and 8 weeks. Tretinoin achieved statistical significance at 8 and 12 weeks ($P=.04$ and $P=.004$, respectively).

Skin tone degradation

There was a statistically significant reduction in average severity scores from baseline in Skin Tone Degradation for AHA-Ret at all time points: 23.3%, 30.0%, and 33.3% ($P<.0001$, all). AHA-Ret demonstrated superior reduction in average severity of Skin Tone Degradation vs retinol at 4 weeks ($P<.0097$). Tretinoin achieved statistical significance through week 12 ($P=.02$, $P<.0001$, and $P<.0001$, respectively).

Pore size

Statistically significant reductions in average severity scores from baseline in Pore Size for AHA-Ret were 8.3% at 8 weeks ($P=.04$) and 25.0% at 12 weeks ($P<.0001$) (Figure 3C). Retinol failed to generate a statistically significant reduction in Pore Size at any time point. Tretinoin achieved statistical significance at 8 and 12 weeks ($P=.03$ and $P<.0001$, respectively). In a subset of subjects ($n=5$), a quantitative analysis of visible facial pores revealed up to a 26% visible reduction in pore count.

AHA-Ret demonstrated statistically significant increases in Global Improvement from baseline at 4, 8, and 12 weeks ($P<.0001$, all).

There were no statistical differences between the groups in average Global Improvement at 12 weeks.

In a noninferiority test with 10% margins, AHA-Ret was noninferior to retinol in each category over 12 weeks. AHA-Ret was noninferior to tretinoin in each category at 4 and 8 weeks, and in Fine Lines/Wrinkles, Erythema, Dyschromia, and Skin Tone Degradation at 12 weeks.

3.3 | Tolerability

There were 20 reports of adverse events (AEs) in nine subjects; the majority of events were mild and transient and included blemishes, dryness, flakiness, redness, tingling, stinging, burning, and solar sensitivity. There were seven cases of retinoid dermatitis among subjects in the retinol group, all deemed “probably treatment-related”. Six of these subjects switched to AHA-Ret with no further adverse events, and one subject required a 2-week rest period from retinol. Two “possibly treatment-related” AEs involved postinflammatory responses subsequent to eyebrow waxing; both were associated with 1.0% retinol. There were no product discontinuations among subjects in either the AHA-Ret or tretinoin groups.

3.3.1 | Nova meter measurements

AHA-Ret was the only product that demonstrated statistically significant increases from baseline in Hydration at each time point; 11.6% (4 weeks; $P=.04$), 14.5% (8 weeks; $P=.03$), and 14.1% (12 weeks; $P=.01$) (Figure 4). AHA-Ret demonstrated statistically significant improvement in Hydration vs tretinoin at 4 ($P<.04$) and 12 ($P=.006$) weeks. Tretinoin demonstrated decreases in skin Hydration over the 12-week period. Retinol demonstrated a statistically significant improvement in Hydration from baseline only at 4 weeks ($P=.01$).

3.3.2 | Subject self-assessment

Subjects completed a 21-question self-assessment. Subject self-assessments demonstrated tolerability with AHA-Ret vs retinol and tretinoin with 9.7% of subjects in the AHA-Ret group, 12.6% in the tretinoin group, and 47.3% in the retinol group reported

(A)



(B)



(C)



FIGURE 3 Visible reductions at 12 weeks in (A) Fine Lines/Wrinkles, (B) Erythema, and (C) Pore Size (visible pore count reduced from 601 to 444 at 12 weeks)

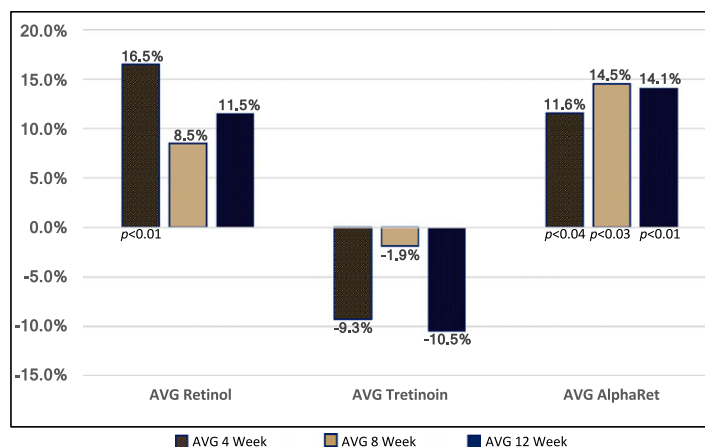
experiencing unpleasant side effects at 12 weeks. AHA-Ret subject self-assessments demonstrated a significantly higher level of tolerability vs retinol at 4, 8, and 12 weeks ($P=.0001$, $P=.0001$, $P=.006$, respectively). Retinol demonstrated the highest amount of reported side effects at all time points. No other substantial differences were demonstrated between products based on subject self-assessments.

4 | DISCUSSION

The cumulative effects of unprotected exposure to the sun and ultraviolet radiation are well documented. Clinical studies have

concluded that half of an individual's exposure to sun and UV radiation occurs prior to age 18;¹⁴ however, the visible consequences of photodamage may not be apparent for decades afterward. While exposure before age 18 is significant, ongoing environmental exposure also contributes to cumulative photoaging from lower intensity, chronic exposure to the UVA spectrum. Recent knowledge suggests that near infrared A and visible light also contribute to premature photoaging. Environmental damage from ozone, airborne particulates, and other types of pollution likely influence the development of wrinkles and pigment dyschromia.¹⁵ The desire to ameliorate the visible effects of photoaged skin, particularly among the large

FIGURE 4 Average percent change in moisture based on Nova meter values



population of “Baby Boomers,” is evident in the explosion of interest in minimally invasive cosmetic procedures.¹⁶ Topical therapies represent an effective and safe approach for facial rejuvenation.

Owing to their established benefits on photodamaged skin, retinoids and AHAs are frequently recommended as part of a topical treatment regimen. Topical retinoids have demonstrated both clinical and histologic efficacy for improving outcomes in photodamaged skin and remain the mainstay for treating photoaging.¹⁷ AHAs have shown significant anti-aging benefits including exfoliation and skin hydration.^{2,3,18} AHA-Ret represents a new category and advancement in skin rejuvenation, effectively combining the benefits of both a retinoid and an AHA in one molecule offering a streamlined approach to skin rejuvenation for photodamaged skin.

The results of this study demonstrate that treatment with AHA-Ret over 12 weeks resulted in early, progressive improvements in the visible signs of facial photodamage, while minimizing the irritation typically associated with retinoids. The value of using a split-face design allows subjects to act as their own controls when assessing for effectiveness and tolerability. AHA-Ret significantly reduced the average severity of Fine Lines/Wrinkles, Dyschromia, Skin Tone Degradation, Erythema, and Pore Size at 12 weeks. AHA-Ret outperformed retinol at 4 weeks with regard to reductions in Fine Lines/Wrinkles, Dyschromia, and Skin Tone Degradation, and induced significantly less Erythema than retinol at 8 and 12 weeks. Significant reductions in Pore Size were achieved in subjects treated with AHA-Ret and tretinoin at 8 and 12 weeks, and were not evident in subjects treated with retinol.

Notably, AHA-Ret was the only product to demonstrate statistically significant increases at every time point in Hydration based on Nova meter measurements and subject self-assessments. Retinol demonstrated statistically significant increases only at 4 weeks with reductions in Hydration occurring at 8 and 12 weeks. Use of tretinoin resulted in decreases in Hydration over the course of the study with the greatest reduction occurring at 12 weeks.

Treatment with AHA-Ret afforded significantly greater tolerability than retinol at all time points. AHA-Ret had lower average reports of unpleasant side effects (9.7%) in comparison with both tretinoin (12.6%) and retinol (47.3%) at 12 weeks with no study discontinuations.

Patient adherence with topical dermatologic regimens is often low particularly when the treatment is poorly tolerated or treatment regimens are complex.^{18–22} The combined efficacy and tolerability profile of AHA-Ret may contribute to enhanced adherence, ultimately resulting in optimal outcomes and high levels of patient satisfaction. This represents a paradigm shift from the traditional “no pain, no gain” approach associated with retinoid therapies. Due to the irritation that often accompanies the use of retinoids, many retinoid products are initially applied every other day (or, every third day) to minimize irritation and potentially reduce discontinuations.^{11,23} In contrast, the unique hydrating AHA-Ret formulation can be used on a daily basis with minimal irritation.

The advanced double conjugation technology behind the AHA-Ret molecule allows for the gradual release of the retinoid and lactic acid into the skin, minimizing the erythema and irritation traditionally associated with retinoid-based products. Inclusion of lactic acid in the AHA-Ret molecule contributes to its hydrating benefits.^{24,25} Additionally, AHA-Ret is formulated with a number of active anti-aging ingredients that further adds to its rejuvenating and moisturizing properties including glycolic acid, multiple antioxidants and peptides, hyaluronic acid, niacinamide, and other beneficial ingredients.

AHA-Ret offers patients an effective, nonprescription retinoid treatment option to counter the visible effects of photodamaged skin while minimizing skin irritation typically associated with retinoid-based products. Further, AHA-Ret’s unique technology facilitates a streamlined treatment strategy to enable once-daily application of a single product that offers the benefits of two complementary, gold standard ingredients. The result is an effective, well-tolerated, hydrating product that affords an early onset of results, potentially facilitating enhanced adherence and maximizing outcomes.

Possible limitations of this study are that it enrolled women that were mostly Fitzpatrick skin type II and was a relatively small sample size. Additional studies that include a broader population may answer questions as to efficacy and tolerability in younger patients, male patients and patients with various skin types. This was an open label trial; however, due to the randomized, split-face trial design, the expert evaluator was not aware of the product being applied to the right or left side of the face. Subjects applied product on a daily

basis, although common practice for retinol and tretinoin “beginners” involves application 2–3 times/wk.

4.1 | Study conclusions

Treatment with a double-conjugate retinoid cream achieved early, progressive improvements in the appearance of Fine Lines/Wrinkles, Dyschromia, Erythema, Skin Tone, Pore Size, and Global Improvement over 12 weeks, and significant improvements in skin Hydration. AHA-Ret induced significantly less Erythema vs 1.0% retinol at 8 and 12 weeks, and was more tolerable than 1.0% retinol and 0.025% tretinoin. Treatment with AHA-Ret, a double-conjugated retinoid cream, represents a new advancement in skin rejuvenation, delivering optimal retinoid efficacy with minimal irritation in individuals with photodamaged skin.

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